Artemisinin-derived dimers from a chemical perspective

Aysun Çapçı¹  |  Lars Herrmann¹  |  Halmuthur M. Sampath Kumar¹,²  |  Tony Fröhlich¹  |  Svetlana B. Tsogoeva¹

¹Organic Chemistry Chair I and Interdisciplinary Center for Molecular Materials (ICMM), Friedrich Alexander University Erlangen-Nürnberg, Erlangen, Germany
²CSIR-Indian Institute of Chemical Technology, Hyderabad, India

Correspondence
Svetlana B. Tsogoeva. Organic Chemistry Chair I and Interdisciplinary Center for Molecular Materials (ICMM), Friedrich Alexander University Erlangen-Nürnberg, Nikolaus-Fiebiger-Straße 10, 91058 Erlangen, Germany.
Email: svetlana.tsogoeva@fau.de

Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: TS 87/16-3; Alexander von Humboldt-Stiftung; Emerging Fields Initiative (EFI) "Chemistry in Live Cells"

Abstract
Considerable progress has been made with the rather recently developed dimer approach, which has already found applications in the development of new effective artemisinin-derived antimalarial, anticancer, and antiviral agents. One observation common to these potential applications is the significant (i.e., much more than double) improvement in activity of artemisinin based dimers, which are not toxic to normal cells and have fewer or less harmful side effects, with respect to monomers against parasites, cancer cells and viruses. Due to the high potential of the dimerization concept, many new artemisinin-derived dimer compounds and their biological activities have been recently reported. In this review an overview of the synthesis of dimer drug candidates based on the clinically used drug artemisinin and its semisynthetic derivatives is given. Besides the highlighting of biological activities of the selected dimers, the main focus is set on different synthetic approaches toward the dimers containing a broad variety of symmetric and nonsymmetric linking moieties.

KEYWORDS
anticancer, antimalarial, antiviral, artemisinin, dimer, hybrid
INTRODUCTION

Artemisinin, along with its derivatives, has become one of the most studied natural products by scientists, especially by chemists. Artemisinin is an enantiomerically pure sesquiterpene containing a 1,2,4-trioxane ring and is a very well-known antimalarial drug, which was isolated from the Chinese medicinal plant Artemisia annua L. (sweet wormwood) in 1972 by Youyou Tu. “For her discoveries concerning a novel therapy against Malaria” Youyou Tu was awarded the 2015 Nobel Prize in Physiology or Medicine.1–3

Biologically more active semisynthetic derivatives of artemisinin (dihydroartemisinin, artemether, arteether, artesunate, artemisone, and artemiside) were developed and they are currently used as first and second line of malaria treatment (Figure 1A).4–8 A functionalization of the prochiral carbonyl at C10 of enantiomerically pure artemisinin leads to two diastereomers. The α- and β-diastereomers of the functionalized artemisinin derivatives can mostly be separated via column chromatography and identified with the different coupling constants J between the two indicated protons (Figure 1B).9 Even though, the endoperoxide unit of the artemisinin is believed to be responsible for the antimalarial activity of artemisinin and its derivatives, the exact mechanism of action of artemisinins is not fully understood yet and molecular targets of artemisinin are still under investigation.10,11

![Figure 1](https://wileyonlinelibrary.com)
encourages artemisinin treatment and research, considerable scientific studies are published every year. However, single usage of artemisinins is discouraged by WHO due to the threat of the development of drug resistance.12

The studies of hybrid antimalarial drugs compared to individual component drugs and to the combination of two drugs have revealed distinct advantages. Hybrid antimalarials are often superior in terms of their efficacy, safety, patient compliance, and pharmacokinetics/dynamics apart from their solubility and stability. To overcome the emerging problem of drug resistance and to further improve the efficacy of artemisinin derivatives, numerous hybrids 13–20 of this unique natural product have been designed, synthesized and evaluated for biological activity by our group21–29 and others.30–37 There has been a resurgence of interest in the synthesis of bivalent ligands capable of improved target binding and protein modulation to derive greater biological responses compared to their monomeric counterparts.

The dimerization concept has also high potential to improve pharmacological properties of the monomeric compounds, reduce toxicity, enhance bioavailability, increase metabolic stability, and might even counteract the problem of drug resistance.38–42 Notably, the structure of the linker moiety proved to be essential for observed efficacies. The artemisinin dimers have significantly increased potency compared to monomers, and were found to have a tumor growth inhibiting capability that was several orders of magnitude higher than monomers.38 This remarkable behavior could be attributed (i) to simultaneous cellular uptake of covalently linked pharcophores in a way that the inhibitory kinetics of the two constituents may amplify each other; (ii) to multivalent binding to protein targets; and (iii) to increased target binding affinities. Artemisinin dimers could also be more stable under metabolic conditions than monomers. Hence, the drug may remain active in the blood stream for a longer time span and reduce parasitemia to crucially lower levels. Another interesting feature of dimers—in contrast to monomers—is their occasionally reduced toxicity, which can be significant. This characteristic may imply that the metabolic pathways in healthy cells and which are affected by the monomers, are less affected by the dimers.38 In this context the dimerization of artemisinin has emerged as a powerful tool for the design of new lead compounds in the field of medicinal chemistry over the last 20 years.38,44–48 The artemisinin dimer approach was primarily aimed at addressing the fact that artemisinins are lipophilic, fast acting but quickly eliminated drugs that are associated with a high rate of recrudescence, when used in monotherapy.

The rationale to design natural product dimers originates from the likelihood that the bivalent dimer can establish thermodynamically stable binding interaction with independent recognition sites of a receptor more efficiently than its monomeric counterpart.49 With this premise, bivalent artemisinin dimers should lead to more efficacious drugs compared to the monomer, when precisely designed considering the required distance between two artemisinin moieties (in terms of spacer arm length and the conformational flexibility).

In our previous review article, we comprehensively discussed the antimalarial and anticancer activities of the artemisinin dimers.38 In other recent reviews, the anticancer activities of dimeric artemisinins and artemisinin hybrids have been summarized.50,51 The present review is primarily focused on the synthesis of artemisinin derived dimers, duly incorporating the literature pertaining to latest developments in this area, along with the biological attributes of prominent leads. The dimers have been categorized according to reaction routes and the way the linker moieties are built up between two artemisinin units.41 The linkers play a crucial role in the modulation of the efficacy of artemisinin dimers. In this review, the dimeric artemisinin derivatives are categorized in different sections based on the linker architecture, covering both symmetric and nonsymmetric linkers (Figure 2). At the end of each section, the antimalarial and anticancer activities of dimers with prominent activity belonging to a particular structural class are discussed. The first category includes dimeric artemisinin derivatives coupled via symmetric linkers whereas in the second category, the dimers were connected via nonsymmetric linkers so that even the identical monomers produce nonsymmetric dimers due to linker dissymmetry. In the third variety of dimers, direct coupling of two artemisinin derivatives devoid of linker, however, the linker is formed by the functional group of artemisinin monomer during the coupling reaction. In all the categories of dimers covered in this review, linkers with enzyme labile functionalities such as esters, phosphonates and sulphate esters apart from varieties of noncleavable spacer arms, both linear or branched, were employed. Dimers synthesized directly from two different
artemisinin derivatives are presented as the fourth category. Apart from nonsymmetric dimers, the examples include symmetric dimers derived from symmetric linker formed during the course of coupling of two different artemisinin derived structural entities.

2 | ARTEMISININ DIMERS CONNECTED VIA SYMMETRIC LINKERS

2.1 | Synthesis

Symmetry is ubiquitous in nature and many symmetric bioactive natural products have been isolated either with evident or hidden symmetry and their total synthesis has been reported.\textsuperscript{52,53} C\textsubscript{2}-Symmetric ligands have been extensively studied for the treatment of several diseases like malaria, HIV, cancer, Alzheimer’s disease, and various parasitic infections. Bivalent ligands are known to be antagonists with improved affinity for opioid (\(\mu/\kappa\)), muscarinic and estrogen/androgen receptors.\textsuperscript{54} Herein, we present symmetric dimers, which were obtained via the reaction of artemisinin derivatives with symmetric linkers (Scheme 1).
In general, all compounds were obtainable by the reaction of an artemisinin derivative with different linkers, whose bare functional groups exhibit opposite reactivity to the applied artemisinin derivative. The functional groups act mostly either as nucleophile (e.g., alcohol or amine) or electrophile (e.g., bromide or acid). The dimers 1a–d (Scheme 2) were obtained by a nucleophilic addition reaction in THF at −78°C between naturally occurring artemisitene and different lithium dithiolates, derived from the corresponding dithiols with varying length of the spacer. For this synthetic method excellent yields were achieved ranging from 86% (for dimer 1a) to 97%

**Scheme 1**  General equation for the synthesis of dimers connected via a symmetric linker [Color figure can be viewed at wileyonlinelibrary.com]

**Scheme 2**  Synthesis of selected dimers 1a–f, 1g/h, 2, and 3
(for dimer 1c). However, the synthesized dimers were not stable and, therefore, decomposition took place in solution or upon storage at room temperature (r.t.). The synthesis of dimers 1e–f turned out to be not as selective as the formation of many products occurred during the performed Grignard reaction between artemisitene and the applied dimagnesiumbromoalkanes as linkers in presence of catalytic amounts of CuBr (Scheme 2).55 The reactions were performed in THF at −78°C and gave the two diastereomeric dimers 1e/1e' in an overall yield of 9% (in ratio of 1:1) and dimers 1f/1f' in an overall yield of 22% (1:3). Dimers 1g/h were synthesized also from artemisitene via a Michael addition reaction with dinitro aliphatic compounds by Barua et al. (Scheme 2).56 After failed attempts to induce the Michael addition reaction with bases like Amberlyst A-21, DBU, triethylamine, or sodium hydride, finally basic alumina supported potassium fluoride was able to trigger the reaction to obtain dimers 1g/h in 40%/46% yields. The dinitro aliphatic linkers were prepared previously from dibromoalkanes in the presence of AgNO3 in water. The C-10 olefinic nonacetal dimers 2a–c were synthesized via a Wittig olefination reaction using a bis-phosphonium ylide as the linker, which was generated in situ by deprotonation of the corresponding bis-phosphonium bromide salt applying lithium ethoxide as base and coupled to artemisinin-derived unsaturated aldehyde (Scheme 2).44 The overall yield for this reaction was nearly quantitative, but the product was obtained as a mixture of three geometric isomers 2a (18%), 2b (27%), and 2c (54%), which were separated from each other via column chromatography and their stereochemistry was determined by 1H-NMR spectroscopy. For the corresponding p-xylene dimers, which were analogously prepared from the aldehyde, decomposition was observed during several hours in CDCl3, and, therefore, these compounds could not be tested for their biological activity. Dimer 3 was prepared with 1,2-ethanediol as linker in the presence of BF3•Et2O as catalyst in dry diethyl ether by utilizing dihydroartemisitene as starting material (Scheme 2).48 The other C-10 saturated nonacetal dimers, besides 2a–c, 4a/b, and 5a/b (Table 1) were prepared from either artemisinin-derived C-10 fluoride via aluminum acetylide condensation using BF3•Et2O as catalyst or from artemether by titanium promoted condensation. The achieved yield for the para-substituted dimer 4a was 27% and for the meta-substituted dimer 4b 19%. It was possible to obtain dimer 5a in 26% and 5b in 33%. By applying SnCl4 as a promoter instead of TiCl4 and dihydroartemisinin-acetate instead of artemether as starting compound, the overall yield was improved to 60% for dimer 5a, which appeared in form of three different diastereomers (5a: β, β 38%, 5a*: a, β 21%, 5a*: a, α 1%).44 These diastereomers were separated chromatographically via preparative HPLC and their stereochemistry was assigned by 1H-NMR spectroscopy. The synthesis of these artemisinin carbodimers were reported without any biological investigations. In 2003, Posner’s group established a synthetic route, in which dihydroartemisinin acetate was converted into dimer 6 in the presence of SnCl4 and an allylic bis-silane linker with 76% yield (Table 1).45 Dimers 7 and 8 were synthesized in the same manner by simply using different bis-silane linker, whereby both products were obtained in decent yields (65%–69%).39,60 The dimer 6 was applied to synthesize a series of other dimers, which will be described later in Section 8. Aromatic diesters 9a–c and aliphatic diesters 10a/b can be prepared in moderate to good yields (58%–75%) by reacting artemisinin-derived alcohol with the corresponding dicarboxylic acid chloride in the presence of catalytic amounts of DMAP.46 Dimers 11a–c, containing an aromatic diether subunit as linker in turn could also be obtained in moderate to good yields (53%–74%) by using a mild reductive etherification procedure, in which artemisinin-derived TMs ether was coupled with an aromatic bisaldehyde at −78°C in the presence of TMSOTf and afterward reduced with Et3SiH.46 The preparation of the phosphate-linked dimers 12a–h on the other hand was accomplished in low to moderate yields (15%–58%) via deprotonation of artemisinin-derived alcohols with sodium hexamethyldisilazide (NaHMDS) followed by addition of the appropriate phosphate dichloride.46,47 Furthermore, the O’Neill group was able to synthesize the bipiperidine-linked dimer 13 in good yield (63%) by treating artemisinin-derived mesylate with 4,4'-bipiperidine in refluxing benzene for 2 days.47 In addition, they successfully accomplished the preparation of the carbonate-linked dimer 14a in good yield (73%) by reaction of an artemisinin-derived alcohol with trichoromethyl chloroformate. In like manner, the reaction with artemisinin-derived amine gave the urea-linked dimer 14b. But unfortunately the reaction led to 14b in only a low yield (18%).47 Dimers 15a–c, 16a–e, and 17a–e, displayed in Table 1 were synthesized by a well-established etherification reaction41 between dihydroartemisinin and the corresponding diols as linkers in the presence of
| Reaction conditions | Dimer via symmetric linker |
|---------------------|-----------------------------|
| **-F**              |                             |
| BF$_3$•Et$_2$O, Et$_2$O, r.t. | para: 4a (27%) and meta: 4b (19%) |

| **-OMe$^{44}$ artemether** or **-OAc$^{48}$** |                             |
| SnCl$_4$, CH$_2$Cl$_2$, $-78^\circ$C | 6 (76%) $^{45}$    |
| 7 (69%)$^{39}$ | 8 (65%)$^{44}$ |

| **-(CH$_2$)$_n$OH** |                             |
| or |                             |
| DMAP, CH$_2$Cl$_2$, r.t. | 9a-c (58%–75%)$^{46}$ |
| n = 2, 3: 10a/b (66%/60%)$^{46}$ |  |

| **-(CH$_2$)$_n$OTMS** |                             |
| (1) TMSOTf, CH$_2$Cl$_2$, $-78^\circ$C | 11a-c (58%–75%)$^{46}$ |

| **-(CH$_2$)$_n$OH** |                             |
| n = 1, 2, 3: |                             |
| X = OMe, OPh, Me | 12a-c (31%–58%)$^{46,47}$ |
| NaHMDS, THF, 0°C | 12d/e (15%/32%)$^{47}$ |
| n = 3: X = OMe, OPh, Me: 12f-h (20%–28%)$^{47}$ |  |

(Continues)
BF₃·Et₂O as catalyst in dry diethyl ether.⁴⁸,⁶² The achieved yields were highly dependent on the used linker, varying from low (9%) to moderate (49%) yields.⁴⁸,⁵⁹,⁶² Surprisingly, the favored stereochemistry for this type of reaction, at the C₁₀ position seemed to be β,β, the only products, which could be isolated from the reaction mixture. For the synthesis of alcohol 15c, an alternative method could be applied: simple reduction of ketone 15b using NaBH₄ as reducing agent and a 2:1 THF/H₂O mixture as solvent afforded product 15c in very good yield (93%).⁴⁸

Preparation of dimers 18a–d was achieved in low yields (12%–20%) by heating (90–110°C) dihydroartemisinin-derived ethylbromide in the presence of different aminoquinoline derivatives in DMF (Table 2).⁶³ In the case of dimer 18d, a quaternary salt was formed, because an aminoquinoline derivative bearing a secondary amine function instead of a primary one was used. Previously mentioned dimer 19 was obtained in 20% yield by a coupling reaction between active ester, formed from artesunic acid and pentafluorophenol (PfpOH), and 1,3-diaminopropane as linker in DMF.⁴¹ An alternative synthetic method was used for the preparation of analogous dimers 20a–c.⁴² This time, direct coupling of artesunic acid and the corresponding diamines was achieved in considerably higher yields (83%–88%) by applying EDC and HOBt as coupling agents and DMF as solvent. EDC was chosen instead of DCC, as no dicyclohexylurea is formed as a byproduct, which consequently leads to an easier work-up of the reaction mixture. In 2006, dimer 21 could be obtained in 47% yield by using a standard ester coupling procedure, where an artemisinin derived alcohol was reacted with malonyl chloride in the presence of dry pyridine at 0°C.⁶⁴ The amide-linked dimer 22 was synthesized by reacting artemisinin-derived carboxylic acid with the corresponding piperazine containing diamine applying EDC and HOBt as coupling reagents.⁶⁵ Copper(I)-
### TABLE 2 Dimers connected via symmetric linkers

| Reaction conditions |
|---------------------|
| DMF, 90–110°C       |
| DMF, r.t.            |
| EDC, HOt, DMF, r.t.  |
| Pyridine, CH₂Cl₂, 0°C|
| HOt, EDC             |

| Dimer via symmetric linker |
|----------------------------|
| X = –(CH₂)ₙNH₂; n = 2–4     |
| X = –(CH₂)ₙN, n = 2–4        |
| or                           |
| n = 1, m = 3, 6, 7;          |
| n = 2, m = 6, 7;             |
| CH₂Cl₂/H₂O, r.t.             |

![Diagram of reaction conditions and dimers](image)

(Continues)
catalyzed azide-alkyne 1,3-dipolar cycloaddition of different aromatic or aliphatic diazides and various artemisinin-derived alkynes afforded dimers 23a–e and 23f/g in 36%–41% yield.66 The reactions were carried out in a mixture of water and CH₂Cl₂ at r.t. using CuSO₄•5H₂O and sodium ascorbate, forming the reactive copper(I) catalyst in situ. Sonogashira cross-coupling reaction between various artemisinin-derived alkynes and different aromatic dihalides afforded dimers 24a–d and 24e–h in 47%–67% yield.67 The reactions were carried out using DABCO as ligand in conjunction with Pd(dba)₂ and Cs₂CO₃ as base in acetonitrile at room temperature. It has to be noted that the stereochemistry of all eight dimers remained intact under these conditions, which was confirmed by ¹H-NMR spectroscopy. Consequently, all dimers showed β-configuration at C-10 position due to the stereochemistry of applied alkynes. In 2003, Jung et al. successfully synthesized C-10 nonacetal dimer 25 in moderate yield (65%) by a nucleophilic substitution reaction between artemisinin-derived bromide and 1,3-propanedithiol in the presence of KOH in DMF. This dimer was not mentioned in our previous review, because no results concerning its biological activity were published from this study in our previous review.38 This dimer 25 was used for the preparation of another dimer, which will be described later in Section 8. In 2015, dihydroartemisinin and C-10 nonacetal arte- misinin alcohol derivatives were coupled with ferrocene dicarboxylic acid chloride in the presence of DMAP to obtain dimers 26a/b in 65%/71% yield.69 Moreover, the first X-ray crystal structure of artemisinin-ferrocene type of dimer was reported and shows that the dimer 26a has α-configuration at C-10 position on both sides of the dimer structure.

In 2017, Magoulas et al. reported new artemisinin dimers with polyamine linkers as potential anticancer agents (Table 2). Three different hydroxyl-functionalized artemisinin derivatives were synthesized before activation. Afterward, activated 10-oxo-artemisinin (A), 10-carba-artemisinin (B), and 11-aza-artemisinin (C) derivatives were prepared with 4-nitrophenyl chloroformate in the presence of Et₃N from hydroxyl-functionalized artemisinin derivatives. Dimerization of the two identical artemisinin active esters derivatives was applied with bistri-fluoroacetate salts of the polyamines (e.g., putrescine) in the presence of Huenig’s base. The symmetric carbamate dimers 27a–c and 27g–i were obtained in 20%–56% yield. Another study based on polyamine-linked dimers was published by Pearce et al. in the late of 2017 (Table 3). In this study, artesunate, the sodium salt of artesunic acid, was used as monomer to synthesize the dimers 28a–j, moreover, dimers were evaluated against malaria parasites Plasmodium falciparum K1 and NF54 strains. Artesunate-polyamine dimers prepared by EDC-HOBt-mediated coupling with Boc-protected polyamines to obtain the dimers 28a–e in 40%–97% yields and with polyamines to obtain the dimers (in other words: tetramer) 28f–j in 43%–71% yield. Tsogoeva et al. reported highly potent bioactive dimer compounds with symmetric linkers in 2015 (Section 6) and 2018 (Section 8).29 The thymoquinone-derived diols were prepared previously from thymoquinone and sodium hydroxyl carboxylate salts.
| TABLE 3 | Dimers connected via symmetric linkers |
|---|---|
| **A** | -O(CH$_2$)$_2$O  
(CH)$_2$OH | Reaction conditions |
| | Putrescine | Dimer via symmetric linker |
| | | R = A, B, C; 27a, 27b, 27c (21%–54%) |
| **B** | -(CH)$_2$OH | i-Pr$_2$NEt, CH$_2$Cl$_2$, 0°C to r.t. |
| | | R = A, B, C; 27g, 27h, 27i (20%–56%) |
| **C** | -N$_{C,11}$-(CH)$_2$O  
(CH)$_2$OH | -OCO(CH)$_2$COONa/ 
artesunate |
| | n = 2, 4, 5, 6, 8; R = Boc  
n = 2, 4, 5, 6, 8; R = Art. acid amide  
EDC, HOBT, DIPEA, CH$_2$Cl$_2$, 0°C |  
-OCO(CH)$_2$COOH/ 
artesunic acid |
| | CH$_2$Cl$_2$, 0°C to r.t. | DCC, DMAP |
| | n = 1, 2: 29a/b (72%/65%)$^{29}$ | |
| | i-Pr$_2$NEt, CH$_2$Cl$_2$ | 0°C - 25°C, o/n |
| | n = 3: 30 (21%)$^{22}$ | |
| | -OCO(CH)$_2$COOH/ 
artesunic acid | (1) EDCI, DMAP in DMF/CH$_3$CN  
0°C to r.t. |
| | (2) Succinic anhydride, DMAP,  
CH$_2$Cl$_2$, 0°C to r.t. | R = H, 31 (54%)$^{72}$ |
| | (3) Dihydroartemisinin, DMF/ 
CH$_3$CN, 0°C to r.t. | R = artesunic acid, 32 (73%)$^{72}$ |
| | | Dihydroartemisinin |
| | Pyridine, CH$_2$Cl$_2$, 4 Å Mol. Sieves,  
0°C - r.t. | 33a (C10,C10'-α,α) (37%),  
33b (C10,C10'-α,β) (21%)$^{72}$ |

(Continues)
using (NH₄)₂S₂O₈ and catalytic amounts of AgNO₃. The dimers 29a/b, which consist of two artesunic acid moieties connected via thymoquinone-derived diols via Steglich esterification, were obtained in 72/65% yield (Table 3). The antimalarial, antiviral and anticancer activity of dimers were analyzed against *P. falciparum*, human cytomegalovirus (HCMV) and sensitive wild-type CCRF-CEM cell line and multidrug resistant P-glycoprotein-overexpressing CEM/ADR5000 leukemia cells. Especially dimer 29a showed significant activity in all cases. Dimer structures were shown in Table 3. Recently, the Tsogoeva group reported the synthesis of several new symmetric artemisinin dimers, 30, 31, 32, 33a/b, and 34a/b derived from artesunic acid or dihydroartemisinin.29,72 Artesunic acid was reacted with glycerol in presence of EDCI/DMAP in DMF/CH₃CN at 0°C overnight, which led to an intermediate artemisinin half-ester in 71% yield. The half-ester led to the dimeric compound 30 upon reaction with one additional mole of artesunic acid in the presence of EDCl/DMAP in DMF/CH₃CN at 0°C in a yield of 54%. Dimer 30 was then reacted with succinic anhydride in DMAP, CH₂Cl₂ at 0°C to ambient temperature to afford dimer 31 in 68% yield. The reaction of dimer 31 bearing the succinyl half-ester with equimolar quantity of dihydroartemisinin in presence of EDCI in DMF/CH₃CN at 0°C to r.t. afforded dimer 32b in 73% yield.72 Dihydroartemisinin was reacted with malonyl chloride in pyridine and CHCl₃ under anhydrous conditions over 4 Å molecular sieves at 0°C for 2 h to give dimer 33a/b in 37%/21% yield. Artesunic acid was reacted with ethylene glycol in the presence of DCC/DMAP, CH₂Cl₂, CH₃CN, r.t. to afford the desired acetylene bridged dimer in near quantitative (97%) yield.73 In a recent publication a symmetric dimer derived from 10-β-Br/β-Cl dihydroartemisinin 36, with dihydroartemisinin β-Br (10%) with dihydroartemisinin β-Cl (10%) was reported.
could be substantially increased by changing the substrate wherein the 10 β-Cl dihydroartemisinin was reacted with piperazine in toluene under inert condition at 0°C for 24 h to afford 35% of the dimeric product.\textsuperscript{74}

### 2.2 Antimalarial activity

The broad variety of dimers with symmetric linkers, summarized in Tables 1–3, exhibited high level of antimalarial activity against chloroquine resistant and chloroquine sensitive \textit{P. falciparum} strains. Out of all symmetric dimers, phosphate ester linked dimers 12a–h exhibited the highest antimalarial activity compared to chloroquine (4700-fold increase) and parent artemisinin (300-fold increase), when tested against both chloroquine resistant \textit{P. falciparum} strains (K1, IC\textsubscript{50} = 0.04 nM) (Figure 3) and chloroquine sensitive (HB3/P3D7, IC\textsubscript{50} = 0.09/0.18 nM).\textsuperscript{46,47} However, the other dimers bearing symmetric linkers viz., dicarboxilic acid ester (10a/b), dibenzoic acid ester/dibenzy ether (9a/11d), diamine (13), carbonate/urea (14a/b) have shown considerably decreased antimalarial activity compared to phosphate ester dimers (IC\textsubscript{50} = 0.46–0.60 nM).\textsuperscript{46,47} Urea linked dimers 14a/b were found to

![Chemical structures and antimalarial activity data]

**FIGURE 3** Overview of the biological activities of selected artemisinin dimers connected via symmetric linkers.
be least active among these compounds (IC\textsubscript{50} > 100 nm). Stable C10 nonacetal dimers were more active (IC\textsubscript{50} < 6.0 nM) compared to labile C10 acetal dimers.\textsuperscript{47} Further, the artemisinin conjugates with conformationally flexible linkers such as aliphatic and cyclohexyl substituted dimers, like 15–17, were more beneficial compared to the dimers bearing phenyl substituted/aromatic subunits on the spacer or with rigid solitary double/triple bond (e.g., 6–8) (IC\textsubscript{50} = 18–77 nM).\textsuperscript{44–46,58} This might be due to ineffective binding of the ligands to the target owing to restriction offered by the rigid spacer compared to their conformationally flexible counterparts. In a recent publication, Tsogoeva's group investigated the action of novel artemisinin derived dimeric conjugates synthesized by them against malaria parasite \textit{P. falciparum} 3D7 strain.\textsuperscript{72} A variety of symmetric dimers developed by them, viz. 30, 31, 32, 33a/b, 34a/b were tested against the \textit{P. falciparum} 3D7 strain. Malonic acid derived isomeric dimer 33a exhibited equivalent activity as dihydroartemisinin and both isomers showed superior activity (33a, EC\textsubscript{50} = 2.4 nM; 33b, EC\textsubscript{50} = 2.7 nM) compared to chloroquine (EC\textsubscript{50} = 9.8 nM) and artesunic acid (EC\textsubscript{50} = 8.9 nM) (Figure 3).\textsuperscript{72} Dimer 34a was the most active compound (EC\textsubscript{50} = 1.4 nM) in terms of antimalarial efficacy and was even more effective than the standard drugs dihydroartemisinin, artesunic acid, and chloroquine (Figure 3). However, when bulky fullerene moieties were conjugated, the activity diminished significantly as seen in case of fullerene substituted dimer 34b (IC\textsubscript{50} = 226 nM). Artesunic acid derived glycerol dimers 30/31 (IC\textsubscript{50} = 4.8/5.4 nM) and a trimer (derived from compound 31) exhibited superior activity (IC\textsubscript{50} = 2.9 nM) than parent compound artesunic acid and chloroquine (Figure 3).\textsuperscript{72} Recently Tsogoeva’s group tested the artesunic acid dimer synthesized by them bearing internal alkyne (35) for on \textit{P. falciparum} 3D7 parasite growth in RBCs, wherein the compound exhibited very impressive EC\textsubscript{50} value of 3.8 nM (Figure 3). Interestingly, this compound also exhibited antiviral properties, when tested on cytomegalovirus (HCMV, EC\textsubscript{50} = 0.94 µM).\textsuperscript{73}

### 2.3 Anticancer activity

Even though artemisinin was first reported as an antimalarial drug, it has been found that dimeric and trimeric artemisinin derivatives exhibit potential anticancer activity compared to their monomeric counterparts.\textsuperscript{57} The last decade has witnessed an increasing number of reports on the antiproliferative potential of dimeric artemisinin compounds and the outcome of this pursuit emphasizes the importance of two trioxane units in the dimer framework for high antitumor activity. Further the studies revealed the important key role played by the linker, significantly impacting the anticancer potential of dimers. Interestingly some of the dimers which exhibited poor antimalarial activity, often exhibited potent antiproliferative activity against specific cancer cell lines, in cell-based assays. This clearly indicates that the biological target of artemisinin for malaria and cancer are obviously different and thus, the mechanism of action differs. Whateverstructure–activity relationship (SAR) established for artemisinin dimers for malaria therapy does not hold well here. Even the dimers with least antimalarial activity may be highly active against specific cancer cell lines. For instance, the symmetric aminooquinoline linked dimers (18b/d) exhibited rather poor antimalarial activity, but when tested against a panel of cancer cell lines, both the hybrids shown GI\textsubscript{50} in the range 0.03 µM (MCF) to 0.08 µM (TK10), surpassing the anticancer potential of etoposide by 74-folds (Figure 3).\textsuperscript{75} Similarly, ferrocene contacting dimers (26a/b), which have poor antimalarial activity, exhibited sixfold higher activity against leukemia CCRF-CEM cells (with IC\textsubscript{50} = 0.07/0.08 µM) compared to parent compound dihydroartemisinin (IC\textsubscript{50} = 0.45 µM).\textsuperscript{69} Phosphate linked artemisinin dimers 12a/b were nontoxic to normal cells (PBMCs) even at concentrations >250 mM, whereas they demonstrated excellent anticancer activity against HL60 cells (IC\textsubscript{50} = 0.07/0.27 µM), far superior to doxorubicin (0.51 µM) and dihydroartemisinin (1.21 µM) (Figure 3).\textsuperscript{46,47} Acetal dimer 16a, which got a score of 36 in NCI mouse hollow fiber assay (paclitaxel score 32 ± 4), was tested on a mouse xenograft model, by subcutaneous administration a of daily dose of 50 mg/kg for 10 days resulting in %T/C of <40%, indicating the compound’s efficacy.\textsuperscript{48} Interestingly, these acetal dimers, which were expected to be less stable under physiological conditions, demonstrated excellent stability under in vivo conditions. Similarly, ether linked dimers 15b/c, which were selectively cytotoxic to leukemia cells, showed no acute toxicity.
Artesunic acid dimer 19 showed excellent antiproliferative activity against leukemia (CCR-CEM, IC50 = 1.2 µM) and multidrug resistant subline (CEM/ADR5000, IC50 = 0.2 µM), when compared to artemisinin and artesunic acid, with promising application as chemotherapeutics against drug resistant tumors (Figure 3).

2.4 | Anti-HCMV activity

In a recent report by Marschall, Tsogoeva and co-workers the mechanism of action of novel artemisinin derived dimeric conjugates against HCMV was investigated. The artemisinin-derived dimer 31 was found to be active against the in vitro proliferation of HCMV with an EC50-value of 1.36 µM exceeding the activity of the reference drugs artesunic acid (EC50 = 5.41 µM) and ganciclovir (EC50 = 2.60 µM) (Figure 3). Despite the high activity of dimer 31, a trimeric compound was found to be more active (EC50 = 0.53 µM). In a first report of its kind by the same team, the target affinity of a selected group of dimeric and trimeric artemisinins was examined by an anchoring to beads. The beads were used for mass spectrometry-based target identification experiments on total lysates of HCMV-infected primary human fibroblasts. Thus, artemisinin-derived dimer 31 immobilized on UV cleavable TOYOPEARL AF-Amino-650M beads were subjected to protein binding studies and two novel cytoskeletal and mitochondrial proteins were identified as target candidates. In this study, major capsid protein (MCP) and envelope glycoprotein (pUL132) were found to be the two putatively ligand-binding viral proteins, which are essential for HCMV replication.

3 | ARTEMISININ DIMERS CONNECTED VIA NONSYMMETRIC LINKER

3.1 | Synthesis

Dimers 37–42 with nonsymmetric linkers (Schemes 3 and 4), reported by ElSohly et al. in 2009,48,62 were synthesized in 7%–72% yield by reacting dihydroartemisinin with 3,5-dihydroxybenzyl alcohol, 3-aminophenol, (R)-(-)-methyl-1,2-ethanediol, (R)-(-)-methyl-1,2-ethanediol, (S)-(-)-1-butene-3,4-diol, and (S)-(-)-1,2,4-butanetriol, respectively, under mild acidic conditions using BF3·Et2O as a catalyst in Et2O (Scheme 4). Dimer 43 was prepared in 61% yield by a coupling reaction between artesunic acid and betulin in the presence of EDC and DMAP in DMF.42 Artemisinin carbodimer 44 was obtained via Michael addition at C-16 of artemisitene with THP protected dinitro compound as linker in 40% yield (Scheme 5).56

In 2016, the groups of Malik and Bhakuni, have reported chalcone-linked artemisinin dimers 45a–e and their anticancer activity (Scheme 6).76 The ethylbromide derivative of dihydroartemisinin was used as a subunit of dimers, which were linked via different chalcone derivatives in the presence of KI and K2CO3 in DMF, at 60–120°C. Dimers were obtained in 30%–75% yield. Antiproliferative effects of dimers 45a/e were analyzed in different human cancer cells by MTT assay. Furthermore, IC50 values of dimer 45d were evaluated in human cancer cell lines HL-60, MiaPaCa, PC-3, HepG2, and LS180. Dimer 45d was found to be more effective than dihydroartemisinin. In the study of artemisinin polyamine dimers 46a–c (described above), one nonsymmetric linker of bistriﬂuoroacetate salts of the protected polyamine, synthesized from N1,N8-ditritylspermidine, has also been applied for the synthesis of dimers 46a–c as described before. Dimer 46a showed very low efficacy, whereas dimers 46b/c exhibited IC50 ~1 µM against MCF7 cells.70
3.2 | Antimalarial activity

The nonsymmetric dimers (37–42) were tested for their antimalarial efficacy against chloroquine sensitive D6 clone and chloroquine resistant W2 clone of *P. falciparum* (Figure 4). Even though most of these dimers showed strong in vitro antimalarial activity with IC₅₀-values in the nanomolar range (3.0–46.8 nM/D6 clone and 4.2–45.4 nM/W2 clone), none of them could match the activity of dihydroartemisinin despite their superior potency to standard drug chloroquine or the parent compound artemisinin itself.\(^{48,62}\)
### 3.3 | Anticancer activity

The artemisinin dimers (37–42) bearing nonsymmetric linkers were subjected to in vitro cytotoxicity studies on a panel of human cancer cell lines comprising solid tumor type (SK-, MEL SK-OV-3, KB, BT-549) along with noncancerous mammalian cell lines (Vero and LLC-PK1) as control (Figure 4). The nonsymmetric dimers 39 and 40 exhibited moderate to very good cytotoxicity against BT549 cell lines (IC$_{50}$ up to 0.08 mM) with hybrid 40 being 17-fold more active than the clinically used drug paclitaxel (Figure 4). The nonsymmetric dimer bearing botulin 43 showed IC$_{50}$-values down to 43 mM, when tested against leukemia cells (CCRF-CEM) and multidrug resistant subline (CEM ADR5000) (Figure 4). Even though the cytotoxicity was higher than the parent compound betulin, it was less toxic than artesunic acid.41

### 4 | ARTEMISININ DIMERS USING DIRECT COUPLING OF TWO IDENTICAL ARTEMISININ DERIVATIVES

#### 4.1 | Synthesis

In general, the synthetic approaches in the Sections 4 and 5, can be divided into two parts: one is the combination of two molecular parts form the same artemisinin-derived precursors (Scheme 7/Section 4) to obtain a dimer, the other...
option is the reaction of two different artemisinin-derived precursors to gain the dimer (Scheme 8/Section 5). The details of these two types of conversions are displayed in Tables 4 and 5. Artemisinin dimers 47a–g (Table 4) linked via C-16 were synthesized by the nucleophilic addition of the corresponding Grignard reagent (RMgBr) to artemisitene followed by the reaction of the formed enolate with a second molecule of artemisitene at −78°C in THF.55 The yields of these reactions were only in the range of 9%–35%, which was probably due to the preference for the mono-addition product. The first step in the preparation of artemisinin-triazine dimers 48a–f was the synthesis of a triazine amine by the reaction of cyanuric chloride with the relevant amines.77 Next, a microwave reaction between this precursor and artemisinin ethyl bromide derivative in the presence of K2CO3 in DMF afforded the desired dimers. The conversion into oxalate salts was performed to increase the stability and solubility, but simultaneously reduced the yields (2.5%–11%).

The synthetic procedure for dihydroartemisinin dimers 49a/b adopted in 199778 and 1998,79 was already published in 1980s:3 To a solution of dihydroartemisinin in Et2O, the Lewis acid BF3·OEt2 was added and the solution was stirred at r.t. A bis nucleophilic coupling reaction between bromoalkyldeoxoartemisinin and sodium sulfide in ethanol afforded sulfur linked dimer 50 (Table 4) in 76% yield.68 A solution phase peptide synthesis approach was applied to prepare dimers 51a–e (Table 4). At first, 10-β-carboxyalkyldeoxoartemisinin was coupled to a N-(2-aminoethyl) glycine derived precursor in DMF using HATU as the coupling reagent. Afterward, the N- or C-terminus of precursor was deprotected, respectively using 20% piperidine/DMF or TFA/CH2Cl2 and a coupling reaction between both molecules led to dimer 51b that was evaluated for its anticancer potential. Via removal of the Fmoc group dimer 51a was
TABLE 4  Direct coupling of two identical artemisinin derivatives

| Reaction conditions | Products |
|---------------------|----------|
| (1) RMgBr, CuBr      | THF, −78°C | R = (CH₂)nX, n = 1–4; X = CH₃: 47a–d (9%–21%)\(^{55}\) |
|                     |          | n = 3; X = Ph: 47e (35%)\(^{55}\) |
| (2) H⁺, H₂O         |          | R = p/m-fluorophenyl: 47f/g (4%/15%)\(^{55}\) |
| (1) K₂CO₃, DMF, microwave (60 W, 50°C, 4 min); (2) 0°C; (3) repetition of step 1 and 2 till the reaction is completed (TLC control) | Dihydroartemisinin α,β: 49a (quantitative yield) β,β: 49b\(^{78,79}\) |
| BF₃•Et₂O, Et₂O, r.t. | Na₂S, EtOH, r.t. | Na₂S, EtOH, r.t. | (Continues) |
obtained and its free amine group was applied for the formation of a new amide bond with a lysine monomer yielding dimer 51c. Dimers 51d/51e were accessible from dimer 51c by different deprotection procedures. In 2005, Fabienne Grellepois et al. synthesized dimer 52 by a self-cross metathesis reaction of the monomer in the presence of Grubbs catalyst in 83% yield. The E/Z ratio for dimer 52 was 90:10. Encouraged by the fact that the endoperoxide bridge remains intact during this metathesis reaction, they transferred the synthetic procedure to other monomers and obtained dimers 53a and 53b in 69% and 50% yield (Table 4). In the case of dimer 53a only the E-isomer was isolated, when a 2nd generation Grubbs catalyst was applied. In 2016 the highly active antiviral artemisinin-isoquinuclidine and artemisinin-carbobicycle dimers 54a-d (Table 4) were prepared via metal-free six-step domino reaction by the Tsogoeva group. The unique linkers of these dimers were obtained from two simple precursors (aldehyde and malononitrile) in one operation. 

(1) 2,6-lutidine, HATU, DMF, r.t.
(2) Piperidine/DMF

R = H: 51a
R = Fmoc: 51b (88%)
For 51c-e: R =
Y = Fmoc, X = Boc: 51c (50%)
Y = Fmoc, X = H: 51d (73%)
Y = H, X = H: 51e (92%)

n = 1; X = O
n = 0; X = CH-OH

Imidazole, toluene, r.t.
4.2 | Antimalarial activity

The dimers 47a–g, linked through the C-16 potion of trioxane containing artemisinin moiety, were found to be more active (IC50 < 5 nM) than artemisinin (IC50 = 12.1 nM) when tested against the P. falciparum strain K1. Besides their activity, the compounds were highly selective as they exhibited no toxicity on Vero cells (Figure 5).

4.3 | Anticancer activity

MTT assay of the artemisinin dimers 49a/b clearly revealed the importance of the stereochemistry of artemisinin dimers for their cytotoxic properties (Figure 5). Compound 49a, the α,β-dimer, (IC50 = 0.35 µM) shows a 20-fold increase in cytotoxicity compared to β,β-dimer 49b (IC50 = 7.2 µM), which shows comparable cytotoxicity to parent compound artemisinin (IC50 = 11.5 µM), when tested against EN2 tumor cells.

The sulfur bridged artemisinin dimer 50 (Figure 5) exhibited high activities, when tested for in vitro cytotoxicity against a panel of human cancer cell lines. The highest activity was found for MCF-7 (IC50 = 0.027 µM) but also high cytotoxicity was observed against P388, EL4, HT-29 (IC50 < 1.0 µM) and moderate cytotoxicity against A549, SKV3, SK MEL2, XF498 (IC50 = 4.9–7.6 µM). Even though the cytotoxicity observed against the oral cancer cells YD-10B was impressive (IC50 = 9.3 µM) compared to clinically used standard drugs like paclitaxel (IC50 = 13.1 µM), 5-fluorouracil (IC50 = 17.3 µM) or cisplatin (IC50 = 14.7 µM), a high level of toxicity of this dimer on normal cells, as revealed by CAM assay, obviates its further development as anticancer lead.

---

**FIGURE 5** Overview of the biological activities of selected artemisinin dimers using direct coupling of two identical artemisinin derivatives
The investigation of dimers 51b–e (Figure 5) revealed that an aminoethyl glycine backbone connected to C-10 nonacetal deoxy artemisinin phenomenally improved the cytotoxicity of the compound in CACO-2 cells. All four dimers 51b–e showed IC$_{50}$-values between 2.04 and 8.03 µM. The study also provided possibilities for further improvement of cytotoxicity by introducing lysine on the backbone as seen in hybrid 51d (IC$_{50}$ = 2.04 µM). The preliminary growth inhibitory activities of dimer 52 and 53b were tested at the NCI. Both were found to be selective and effective against leukemia (HL 60), non-small-cell lung cancer (NCI-H226), colon cancer (COLO-205 and KM-12) and CNS cancer (SF-295) cell lines.

5 | ARTEMISININ DIMERS USING DIRECT COUPLING OF TWO DIFFERENT ARTEMISININ DERIVATIVES

5.1 | Synthesis

In the following, reactions of two different artemisinin precursors leading to dimer molecules will be discussed (Scheme 8). Dimer 55a (with an aromatic methoxy unit) and dimer 55b (containing a furan moiety) were synthesized by a Friedel–Crafts condensation between artemisinin-derived C-10 fluoride and the corresponding aromatic artemisinin derivative (Table 5). The reaction was performed in CH$_2$Cl$_2$ at −78°C applying BF$_3$·OEt$_2$ as the Lewis acid. Dimer 55a was isolated in 74% and dimer 55b in 56% yield. Compared to the other dimers of this study, compound 55a and 55b were the only dimers with an α-linkage. Amide dimer 56, introduced by Chadwick et al. as part of their C-10 carba artemisinin dimer study, was prepared in 74% yield by the reaction of artemisinin derived acid chloride and artemisinin derived amine in the presence of Et$_3$N in CH$_2$Cl$_2$. Applying coupling reaction conditions (HOBt, EDC, CH$_2$Cl$_2$, r.t.) for artemisinin derived amines and artemisinin derived acid, dimers 57a/b (Table 5) were received in up to 81% yield. Additionally, the synthesis and biological evaluation of dimer 60 was reported in this publication. First, the precursor was converted into amide linked dimer 59 using protected glutarate, HOBt, EDC in CH$_2$Cl$_2$ at r.t. (84% yield). Next, the protecting group was removed and a coupling reaction between compound 58 and 59 (see Table 5) led to dimer 60 in 51% yield. In 2011, Xie et al. presented a study of artemisinin-guanidine dimers, including dimers 61a–h (Table 5). These dimers were obtained by a four component aza-Wittig reaction in yields between 28% and 43%, using azide, amine (synthesized from azide by a Staudinger reaction), substituted isocyanatobenzene and PPh$_3$ (Table 5). Saikia et al. demonstrated that the copper(I) catalyzed 1,3-dipolar cycloadition is suitable for the synthesis of different artemisinin derivatives. Using “click chemistry,” the 1,2,3-triazole-containing artemisinin dimers 62a/b (Table 5) were obtained. In the course of the reactions, alkyne and azide precursors were accessible in one step from dihydroteartemisinin. The precursors were stirred in a mixture of CH$_2$Cl$_2$/H$_2$O in the presence of CuSO$_4$·5H$_2$O and sodium ascorbate and dimers 62a/b were obtained after purification in 39%–37% yield. In addition, the Ugi reaction is compatible with artemisinin compounds as well: Wang and Sasaki applied the Ugi reaction to synthesize dimers 63a–g. Methyl isocyanoacetate, the appropriate alcohol/acid and the artemisinin precursors, aldehyde and amine, were reacted with each other in MeOH (Table 5). The corresponding dimers were obtained in yields between 22% and 68%. As the highest diastereomeric excess for a dimer was only 33%, further optimizations were specified as in progress. Artemisinin derived ketone 64, a valuable precursor for many dimers introduced hereafter (Section 8), contained the

![Scheme 8](https://wileyonlinelibrary.com)
| Table 5 | Direct coupling of two different artemisinin derivatives |
|---------|--------------------------------------------------------|
| **FG1** | **FG2** | Reaction conditions |
| (CH2)2-NH2 | (CH2)2-CO-Cl | Et3N, CH2Cl2, 0°C to r.t. |
| (CH2)2-NH2 or (CH2)4NH2 | (CH2)2-COOH | HOBt, EDC, CH2Cl2, r.t. |
| O-CH2-N3 | O-CH2-NH2 | Substituted isocyanatobenzene, PPh3, 60°C |
| O-CH2-CCH or O-(CH2)2-CCH | N3 | CuSO4 Sodium ascorbate, CH2Cl2/H2O, r.t. |

| Reaction conditions | |
|---------------------|---|
| BF3•OEt2, Et2O, −78°C | |
| Et3N, CH2Cl2, 0°C to r.t. | |
| HOBt, EDC, CH2Cl2, r.t. | |
| (1) HOBt, EDC, CH2Cl2, r.t. | |
| (2) TFA, CH2Cl2, 0°C | |
| CuSO4 Sodium ascorbate, CH2Cl2/H2O, r.t. | |

(Continues)
reaction between artemisinin derived TMs enol ether and acetylated dihydroartemisinin in the presence of SnCl₄ in CH₂Cl₂ at −78°C as the last step in its synthesis route. Taking into consideration the yield of this step with 69%, ketone 64 was synthesized from artemisinin in five linear steps with an overall yield of 36%.

Tsogoeva and co-workers reported the C-10 acetal and C-10 non acetal ester-linked artemisinin dimers 65a and 65b, which were synthesized via DCC/DMAP mediated coupling reaction in 57% and 68% yield (Table 5). The dimers 65a and 65b were screened for the activity against P. falciparum, HCMV and human leukemia cell lines. In 2017, Vu et al.
reported amide-linked artemisinin dimers 66a–g with seven different linkers. Amine and carboxylic acid derivatives of artemisinin were synthesized from dihydroartemisinin. First, dihydroartemisinin was converted to the azide derivative in 45% yield before the artemisinin-amine derivative was obtained from this azide via Staudinger reduction in 81% yield. Amide coupling of amine with succinic acid, glutaric anhydride, 3,3-dimethylglutaric anhydride, maleic anhydride and naphthalic anhydride using EDC, HCl, DMAP in CH2Cl2 succeeded in 70%–86% yield, whereas coupling with adipic acid monomethyl ester and suberic acid monomethyl ester followed by hydrolysis was achieved in 74%–80% yield in two steps. Dimerization of obtained seven carboxylic acid derivatives with amine derivative, applied in the presence of EDC, HCl and DMAP at r.t. gave 68%–76% yield. Dimers 66a–g were tested against cancer cells HepG2, MCF-7, and HL-60. Notably, the dimer 66d with a double bond linker was reported the most active compound in the series.

5.2 | Antimalarial activity

Symmetric C10 nonacetal dimers 55a and 55b (Figure 6) bearing rigid dimethoxyphenyl and furyl bridge respectively, were found to be highly active with IC50 values of 1.3 and 3.2 nM against P. falciparum strain NF54. Symmetric dimers 48e/f (Table 4) obtained through direct coupling, with variation of the substitution on 1,3,5 triazine unit, were found to be comparatively less active (IC50 = 5.5–35.9 nM), but partly still were potential antimalarial compounds. Compound 56 (Figure 6) bearing aliphatic amide linkage between two artemisinin moieties exhibited 400-fold higher potency than artemisinin (IC50 = 0.03 nM vs. 12.3 nM for artemisinin and 2.11 nM for artemether), when tested on P. falciparum strain NF-54. This is in contrast to the comparably less active symmetric dimers 55a and 55b, which had rigid aryl and furyl bridges between the artemisinin moieties, thereby highlighting the role of flexibility of linker in influencing the antimalarial activity of the dimer (Figure 6).

5.3 | Anticancer activity

Most of the artemisinin dimers listed in Table 5, under this category exhibited anticancer activity with IC50 value <1 µM and amide dimer 57a was found to be most active with IC50 of 8 nM for breast cancer MCF-7 cells against P. Falciparum NF-54
55a IC50 = 1.3 nM
55b IC50 = 3.2 nM

against P. Falciparum NF-54
56 IC50 = 0.03 nM

against human cancer cell lines
57a (n = 2) MCF-7 IC50 = 8 nM
57b (n = 4) MCF-7 IC50 > 20 nM

Ar = 2-chloro-5-(trifluoromethyl)phenyl: 61f
against human cancer cell lines
MDA-MB-231: IC50 = 1.42 µM
A549: IC50 = 0.24 µM
HT-29: IC50 = 1.4 µM

62a/b (n = 1/2)
activity against colon HST

FIGURE 6 Overview of the biological activities of selected artemisinin dimers using direct coupling of two different artemisinin derivatives
(Figure 6). In yet another study, this compound was tested against a panel of five cancer cell lines, viz., A-549, SK-V-3, SK-MEL-2, XF498, HCT-15. The dimer was found to be active against all the cell lines, however, less active than doxorubicin and dihydroartemisinin. The compound showed moderate activity (48%), when subjected to CAM assay to verify its antiangiogenesis potential. It outperforms artemisinin and dihydroartemisinin (25%), but is less active than standard drug thalidomide (55%). On the contrary, compound 57b with similar structure as 57a but with elongated chain length exhibited considerably reduced cytotoxicity, showing the influence of chain length on the ensuing cytotoxicity of dimer (Figure 6).

Amide dimer 56 was found to be most active with IC$_{50}$ of 0.1 µM for HL60, showing the compound to be comparatively more active than dihydroartemisinin (IC$_{50}$ = 2.1 µM). Guanidine linked dimers (61a/h) were subjected to cytotoxicity evaluation against a panel of three cancer cell lines and the compounds demonstrated potential cell killing across the board with highest cytotoxicity with dimer 61f bearing 2-chloro, 5-(trifluoromethylphenyl) substitution on guanidine framework with IC$_{50}$ values of 1.42 µM (MDA-MB-231), 0.24 µM (A549), and 1.4 µM (HT-29) (Figure 6). Trioxane dimers 62a/b demonstrated impressive growth inhibition of cancer cells with two-fold higher inhibition (62a, 63% and 62b, 70%) with colon HCT cells compared to artemisinin (37%). Dimer 62b also exhibited superior anticancer activity than artemisinin against leukemia THP-1 (79%) and lung A-549 cells (48% growth inhibition vs. 29% for artemisinin) (Figure 6).

6 | ARTEMISININ DIMERS DERIVED FROM OLEFIN 67

6.1 | Synthesis

In 2003, Posner’s group published a very important synthetic route, where artemisinin was converted in two steps into olefin dimer 67 (Figure 7), which was used as starting material for the synthesis of many different dimers (Scheme 9). Vicinal diol dimer 68 was prepared in high yield (92%) by dihydroxylation of olefin dimer 67 using 4-methylmorpholine N-oxide and catalytic amounts of osmium tetroxide in acetone at r.t. Starting from 68, the dimer 69 was prepared by Posner et al. in high yield (93%) by a hydroboration reaction and in situ oxidation of olefin dimer 67 using a borane dimethyl sulfide complex and sodium perborate in dry THF at r.t. This alcohol dimer proved to be a very important precursor among artemisinin-derived dimers, as it was a promising active antimalarial substance and was also converted, like olefin 67, into a series of other artemisinin-derived dimers (Scheme 10). Ketone dimer 70 was synthesized in 70% yield by oxidative cleavage of the double-bond present in olefin dimer 67, using catalytic amounts of osmium tetroxide and oxone, and was afterward reacted with styryllithium to afford styryl tertiary alcohol dimer 71 in 74% yield. Afterward, this dimer was oxidized by utilizing KMnO$_4$ to the desired benzoic acid dimer 71′ in 50% yield. An alternative synthetic method for the preparation of ketone dimer 70 was published five years later in 2008 by Posner et al. Preparation of hydrazine dimer 72 was accomplished in 86% yield by reaction between ketone dimer 70 and isoniazid in the presence of p-toluene sulfonic acid. The reaction between dimethyldioxirane (DMDO) and olefin dimer 67 in anhydrous CH$_2$Cl$_2$ formed
SCHEME 9 Synthesis of dimers via post modification of olefin 67
SCHEME 10  Synthesis of dimers via post modification of alcohol 69

**Scheme Details:**

1. **Reagents and Conditions:**
   - PhNH₂, NaBH(OAc)₃, CH₂Cl₂, r.t.
   - RCl, LHMDS, THF, 0 °C to r.t. or RCl, NaH, CH₂Cl₂, r.t.
   - 4-methylbenzyl bromide, N₃, DMF, r.t.
   - Pyridine, DMAP, CH₂Cl₂, r.t.
   - PPh₃, CBr₄, CH₂Cl₂, r.t.
   - 1. RSH, NaH, DMF or CH₂CN
   - 2. mCPBA or DMD

2. **Yield:**
   - 85 62%
   - 84 59%
   - 87 77%
   - 88 68%
   - 89 67%
   - 90 73%
   - 91 41%
   - 92hvi 26%/34%
   - 92j 56%

3. **Additional Notes:**
   - X = N-O: 83a 96%
   - X = N: 83b 91%
   - \( R = -PH\) 
   - \( R = -E\) 
   - \( R = -IP\) 
   - \( R = -Cl\) 
   - \( R = Ph-2,6-DMe\) 
   - \( R = Ph-2,6-iPr\) 
   - \( R = Ph-4-Cl\) 
   - \( R = Ph-O\)

4. **Chemical Structures:**
   - [Diagram of synthetic pathway with chemical structures labeled accordingly]
epoxide dimer 73 in good yield (80%), which was then converted to β-hydroxysulfide dimer 74 in 80% yield via a reaction with a substituted benzenethiol in presence of chromatographic alumina. After two additional reaction steps involving oxidation of sulfide dimer 74 to sulfone dimer 74′ (76%) and basic saponification (79%), the benzoic acid dimer 74″ was obtained in overall good yield. In 2013, Sasaki et al. synthesized the piperazine trioxane dimers 75a–d in moderate to good yield (53%–81%) via nucleophilic ring-opening reaction of epoxide dimer 73 using various different piperazine derivatives as nucleophiles in the presence of LiBr as mild Lewis acid (Scheme 9). It has to be noted that for the preparation of the epoxide dimer 73 an alternative method was applied: Instead of DMDO, meta-chloroperbenzoic acid (mCPBA) was used as oxidizing agent and the final product was used without further purification, therefore no yield was determined. By using RuCl₃ and NaIO₄ as an oxidizing agent and diol dimer 68 as starting material it was possible to increase the yield from 70% to 81% (Scheme 9). Dimers 76a could be obtained in good yield (77%) by Williamson like ether synthesis using alcohol dimer 68 and the corresponding aromatic halide: 4-nicotinephyl chloride hydrochloride (Scheme 9). The reaction was performed in the presence of either NaH as base and DMF as solvent. A similar reaction with diol dimer 68 afforded ether dimer 76c in relatively low yield (36%). This time KH was used as base, THF as solvent and instead of an organic halide, the corresponding tosylate (2-butyne-1-tosylate-4-p-fluorobenzyl ether) was applied. Benzoic acid ester dimer 76b was synthesized in 80% yield by standard ester coupling using benzoyl chloride and diol dimer 68 as starting compounds and pyridine as base. The alcohol dimer 68 was converted into water soluble carboxylic acid dimer 77 (Scheme 9) to gain a compound that can be easily administered in vivo. Ring opening of succinic anhydride by alcohol 68 in the presence of DMAP afforded the desired product 77 in high yields (85%) (Scheme 9).

P-formaldehyde or various different cyclic ketones were reacted with diol dimer 68 in the presence of p-toluensulfonic acid to form the dimeric artemisinin-derived ketals 79a–h in moderate to nearly quantitative yield (54%–96%).

The alcohol dimer 69 was, analogue to dimer 68, converted into water soluble carboxylic acid dimer 80 (Scheme 10) to gain a compound that can be easily administered in vivo. Ring opening of succinic anhydride by alcohol 69 in the presence of DMAP afforded the desired product 80 in high yields (84%) (Scheme 9). Isonicotinate ester dimer 83a could be obtained in high yield (91%) by esterification of primary alcohol dimer 69 with isonicotinic acid by applying EDC and DMAP as coupling agents and dry CH₂Cl₂ as solvent. In 2004, Posner et al. used alcohol dimer 69 to synthesize two novel dimers: isonicotinate N-oxide dimer 83a and aldehyde dimer 84 (Scheme 10). Isonicotinate ester dimer 83b could be obtained in high yield (91%) by esterification of primary alcohol dimer 69 with isonicotinic acid by applying EDC and DMAP as coupling agents and dry CH₂Cl₂ as solvent. Isonicotinate N-oxide dimer 83a was synthesized in the same manner as isonicotinate dimer 83b in nearly quantitative yield (98%). The aldehyde derived dimer 84 was prepared in 59% yield by standard oxidation reaction of primary alcohol dimer 69 utilizing pyridinium dichromate as oxidizing agent and CH₂Cl₂ as solvent. Reductive amination of this aldehyde dimer by using aniline as primary amine and sodium triacetoxyborohydride afforded the desired amine dimer 85 in 62% yield (Scheme 10). Thiophosphate ester dimer 86a was prepared in 56% yield by ester coupling reaction in THF between primary alcohol dimer 69 and diethyl chlorothiophosphate in the presence of lithium hexamethyldisilane. A similar reaction between diethylcarbamyl chloride and alcohol dimer 69 formed carbamate dimer 86b in 70% yield, but this time NaH was used as base and CH₂Cl₂ as solvent. The dimer 87 (77%) was obtained by Williamson like ether synthesis in THF using alcohol dimer 74, the aromatic halide 4-methylbenzylbromide and sodium hexamethyldisilazane (NaHMDS) as base (Scheme 10). Aforementioned dimer 88 was synthesized in 68% yield by Morrissey et al. in 2010 by reaction of the alcohol dimer 69 with tetrafluorophenol in the presence of EDCI/NEt₃ and was further reacted with hydrazine to obtain dimer 88. Carboxylic acid dimer 89, which can be obtained in high yield (87%) by oxidation of alcohol dimer 69 using NaIO₄ and RuCl₃ as oxidizing agent, was also used later on for a series of modification steps (Scheme 11). In 2009, Hartwig et al. published the synthesis of aforementioned fluorescent dansyl trioxane dimer 90 and coumarin trioxane dimer 91. Dimer 90 was prepared in good yield (73%) by sulfonylation reaction of dansyl chloride with alcohol dimer 74, which was conducted in CH₂Cl₂ in the presence of Et₃N. Dimer 91 was synthesized in decent yield (41%) by Steglich esterification reaction between bis trioxane primary alcohol dimer 69 and 7-dimethylamino-coumarin-4-acetic acid with the coupling agents DCC and DMAP. Aforementioned phosphite dimers 92a–i could be obtained in low to nearly quantitative yield (25%–96%) by reaction of primary alcohol...
dimer 69 with the appropriate phosphoryl chloride in CH₂Cl₂ at room temperature in the presence of pyridine and DMAP as bases (Scheme 10). Standard ester hydrolysis of diphenylphosphate ester dimer 92a in DMF at 50°C afforded monophenylphosphate ester dimer 92j in 59% yield. Additionally, Posner established a synthetic route for the preparation of several different sulfone trioxane dimers 94a–f (Scheme 10). At first, alcohol dimer 69 was converted into the primary bromide dimer in good yield (86%) by applying PPh₃ and CBr₄ as reagents in CH₂Cl₂. Afterward, sulfone dimers 94a/b and 94f were prepared in overall fair yields (51%/67%). First, the primary bromide was treated with different thiols in the presence of NaH forming the corresponding thioether dimers, which then were used in the next step without purification as crude mixture and oxidized with either m-chloroperoxybenzoic acid (mCPBA) or DMDO to the desired products (Scheme 10). Sulfone carbamate dimers 94c/d and sulfone phosphate dimer 94e could be obtained in moderate to good yield (37%–76%) by coupling reaction between sulfone benzylic alcohol dimer 94b and either the appropriate carbamyl chlorides or diethyl chlorophosphate in the presence of either NaH or pyridine as base. Dimers 95a–c were synthesized in moderate to good yield (59%–88%) by standard amide coupling reaction between carboxylic acid dimer 89 and the corresponding primary amines or isoniazid using EDC, HOBt and Et₃N as coupling agents and CH₂Cl₂ as solvent (Scheme 11). Additional amide dimers 95d–j were prepared in an analogous manner by Posner et al. in 2007 and 2008. The achieved yields ranged from moderate to quantitative (54%–100%). In the same year, the group of Posner also published the synthesis of two oxadiazole dimers 96/97, obtainable in moderate yield (40%/62%) by
reaction of carboxylic acid dimer 89 with either 4-fluorobenzohydrazide or N-hydroxyethanimidamide in the presence of DIC and HOBt in DMF. Sasaki et al. prepared the dimers 99a and 99b, starting from carboxylic acid dimer 89. At first, trioxane dimer hydrazide 98 was synthesized in 68% yield by a coupling reaction between anhydrous hydrazine and carboxylic acid dimer 89 using tetrafluorophenol, EDC and Et3N. Afterward, hydrazide dimer 98 was reacted with the appropriate aldehyde to form the desired products 99a (96%) and 99b (Scheme 11).

6.2 | Antimalarial activity

Most of the dimers derived from olefin 67 were active against *P. falciparum*. The dimers 68, 89 and 83a were most active against the chloroquine sensitive strain NF-54 (IC50 = 0.53–3.0 nM), when compared to the precursor olefin 67 (IC50 = 24 nM) (Figure 8). Among these compounds, alcohol dimer 68/69, ketone 70 and isonicotinate N-oxide dimer 83a were most active with an IC50 < 1 nM. These dimers were 18-folds more active than artemisinin and threefold more active than sodium artesunate. However, under in vivo conditions, compound 77, 80, and 70 show higher activity, when administered intravenously to *Plasmodium berghei* (10 mg/kg). The compounds suppressed the parasite load by 80% and were found to be more efficacious than the sodium artesunate administered orally. All three compounds were found to be free from toxic side effects. Similarly compounds 89 and 83a also exhibited better efficacy when administered orally or intravenously to *P. berghei*. However, compound 89 being least toxic was found to be the best option. Compounds 81a/b, 86a/b, 94c and 95a/c/d synthesized by Posner et al., outperformed the clinically used drugs sodium artesunate and artemether, when subjected to in vivo screening. The compounds brought down the disease burden of *P. berghei* by 100% when administered orally (1 × 10–144 mg/kg) or intradermally (3 × 10–30 mg/kg). The dimers show no noticeable side effect post treatment.

**FIGURE 8** Overview of the biological activities of selected artemisinin dimers derived from olefin 67.
The SAR analysis of compound 95b and 95j (Figure 8) compared to the rest of the analogues studied by the Posner group reveal clearly that lipophilic substitution on the amide side chain, for example, with t-butyl or trimethylsilyl groups, greatly favored the antimalarial efficacy of the drug rather than having an aromatic substituent on the side chain.87,94 Excellent results were obtained, when silyl amide trioxane dimer 95j (Figure 8) was administered orally in a single dose (8 mg/kg in combination with mefloquine hydrochloride (24 mg/kg) to malaria infected mice, wherein the infection could be completely reduced by 100% without any side effect.94 Similar results were obtained for the sulfone trioxane dimer 94b/c suppressing the parasitemia by >99.9% within 3 days of administration to mouse at relatively low doses (54 mg/kg) in combination with mefloquine hydrochloride (13 mg/kg) (Figure 8).93

6.3 | Anticancer activity

Several of the olefin derived artemisinin dimers displayed excellent cytotoxicity against a panel of human cancer cell lines. Alcohol dimer 69 shows IC50 values in the range 9.2–23.3 nM superior to clinical drug doxorubicin (IC50 = 28.7–75.9 nM), when tested in vitro on various prostate cancer cells viz., C2H, C2G, C1A, and C2D.89 This dimer has displayed a wide spectrum of activity against other cancer types too. For instance, it exhibits impressive IC50 values of 20/50 nM against leukemia cells CCRF-DEM and LEM/ADR5000; 43 nM against the breast cancer cells TMLn3 and 0.1 mM against colon HCT-116 cells.69 Phenyl substituted secondary amine dimer 85 displayed a high growth inhibition of prostate LnCap cells with GI50 of 17.9 nM compared to doxorubicin (GI50 = 45.3 nM) (Figure 8).40 The sulfone trioxane dimer 94a/c exhibits comparable IC50 values to doxorubicin, when tested in vitro on lymphoma (U-933), leukemia (HL-60), melanoma (SK-MEL5 and UACC-62) and cervical (Hela) cells with IC50 in the range of 0.03–1.1 µM.93 However, the sulfone dimers were found to be safer, when tested on noncancerous fibroblast cells WE-MEF, HS888Lu. The cells were less harmed than for doxorubicin, which revealed toxicity with IC50 of 3.4 µM (WE-MEF) and 1.4 µM (HS888Lu). Phosphate dimers 92a and 92c-j (Figure 8) exhibited high cytotoxicity with IC50 values in the range of 31.9–511 nM on various cancer types viz., leukemia (Jurkat T-ALL), prostate (LnCap, C1A, C2H), colon (HCT-116), cervical adenocarcinoma (HeLa) and melanoma (1205Lu).93,94 However, these compounds bearing dimer 92f were nontoxic to normal cells when tested on PBMCs and HFF noncancerous cells.92 Similarly, the pyridine containing trioxane dimer (88) considerably reduced the proliferation of prostate cancer subtypes (C4-2, LNCap and PC-3) with IC50 values in the range of 10–29 µM barring DU145 cells within 72 h post treatment.93 Dimer 99a (Figure 8), with an analogous structure to 99b (replacing pyridine moiety with phenol), also shows very high cytotoxicity in vitro on rat mammary adenocarcinoma cells (MTLn3) with IC50 values of 43 nM with a sevenfold increase in activity compared to dihydroartemisinin. The dimer could regress the tumor in vivo more efficiently than dihydroartemisinin (p < .01) on mammary adenocarcinoma rats.93,96 A Transferrin conjugate of the hydrazide dimer 98 exhibited superior cytotoxicity to dihydroartemisinin against breast cancer cells (BT474, IC50 < 9 nM) without any toxic manifestation on normal breast cell line (MCF-10A).97 The conjugate considerably down regulates c-MYC and mutated human epidermal growth factor receptor-2 (ERBB2, HER2). The pH dependent soluble piperazine conjugates (75a/d) (Scheme 9) developed by Zhang et al. exhibited high cytotoxicity on breast cancer cells BT-474 and MDA-MB231 with IC50 values in the range of 0.022–0.11 µM with library members displaying excellent cell line specificity.86

7 | ARTEMISININ DIMERS ACCESSIBLE VIA POSTMODIFICATION OF MISCELLANEOUS ARTEMISININ DERIVATIVES

7.1 | Synthesis

In 2002, Posner et al.58 described the synthesis of C-10 tetra fluorinated nonacetal dimers 100a/b obtainable in 16%–28% yield by fluorination reaction of previously mentioned dimer 5a performed at a high temperature in the
presence of commercially available bis-(2-methoxyethyl) aminosulfur trifluoride (BAST) (Scheme 12). Four years later, Posner's group published the preparation of four trioxane dimers 102–104.39 The diene dimer 7 was transformed into phthalate dimer 101 via [4 + 2] Diels–Alder cycloaddition with dimethyl acetylenedicarboxylate followed by dichlorodicyanoquinone oxidation in 54% yield. Standard hydrolysis of bis-ester dimer 101 with LiOH in THF/water mixture led to phthalic acid dimer 102 in 47% yield. Furthermore, phthalate dimer 101 was reduced into bis-benzyl alcohol dimer 103 in 64% yield with the help of DIBAL-H. Bis-benzyl alcohol dimer 103 was phosphorylated either into bis-phosphate dimer 104 (52% yield) or into cyclic phosphate dimer 105 (47%) (Scheme 12). It is also stated that during these reaction steps, the crucial peroxide unit of trioxane stayed intact.39

Elsohly et al. presented dihydroartemisinin acetal dimers 106a/b, 107, and 108a–c which were formed from symmetric ether linked dimers 15a/c (Section 1) or from nonsymmetric ether linked dimer 39 (Section 3).48,57,62 The vicinal diols 106a/107 were prepared by dihydroxylation reaction using osmium tetroxide in very good yields (95% and 99%) (Scheme 13). By epoxidation of olefin dimer 15a with mCPBA, dimer 106b could be obtained in 67% yield. A coupling reaction between alcohol dimer 15c and succinic anhydride afforded carboxylic acid dimer

SCHEME 12   Synthesis of dimers 100–105 via postmodification
In addition, alcohol dimer 15c was sulfonylated with mesyl chloride in dry pyridine. Oxime formation of alcohol dimer 15c with hydroxylamine and NaOAc in refluxing CH$_2$Cl$_2$ gave trioxane dimer 108a. As mentioned before, Moon et al. published a new family of five carbon-linked carboxylate ester dimers 109a–c in 2010 (Scheme 14), which were synthesized from diene dimer 8 using the appropriate carboxylic acid/acid chloride and Et$_3$N/EDC in 65%–83% yield. Diene dimer 8 was also used as starting compound for the synthesis of dimers 106–108 via postmodification.
preparation of triol dimer 110 by a hydroboration and subsequent oxidation (50% yield). By reaction of dimer 110 with different commercially available ortho-esters, dimers 111a–c were obtained in good yields (75%–91%). Bromo ortho-ester dimer 111c was used to synthesize sulfone ortho-ester dimer 111d in 69% yield over two steps by a thiophenoxide displacement of the bromine atom followed by sulfide oxidation. All oximes 112a–f and

**Scheme 14** Synthesis of dimers 64 and 109–116 via postmodification
116a–e, carbonates 114a–o and alcohols/carbamates 115a–n, investigated by Posner et al. for their in vivo antimalarial potential, were accessible from artemisinin derived ketone 64 (Scheme 14). To convert ketone 64 into oximes 112a–f, pyridine and the corresponding hydroxylamine were applied. The six oxime dimers were obtained in a yield range of 72%–81% (yields given for Z isomers).

Ketone 64 was reduced with (R)-CBS-oxazaborolidine and BH$_3•$THF. Thereby alcohol 113 was received in 92% yield with 98% diastereomeric excess, as published in 2014. Applying DIBAL-H as the reducing agent, alcohols 113/113' were obtained in a 1:1 ratio. The alcohol 113' has an inversion in the stereocenter of the newly formed alcohol compared to 113. Having alcohol 113 in hand, a reaction with commercially available isocyanates and Et$_3$N in CH$_2$Cl$_2$ led to carbamates 115a–n in 60%–99% yield. To prepare the carbonates 114a–o, DMAP, pyridine and commercially available chloroformate were mixed and stirred at r.t. Employing this method, the yields ranged between 47% and 98%. Further derivatization of 112a lead to dimers 116a–e with the help of the corresponding halogens and NaH in THF, or with Et$_3$N and the appropriate chlorophosphite in CH$_2$Cl$_2$. This second step (from dimer 64) gave the products in 37%–99% yield.

Sulfone dimers 117a/b were obtained in good (91%) and moderate (72%) yield by the oxidation of disulfide-linked dimers with mCPBA in CH$_2$Cl$_2$ (Scheme 15). Fullerene dimer 118, published by Jung et al., was prepared from dimer 21 (Scheme 15) in the presence of DBU/I$_2$ and fullerene in toluene. After purification via column chromatography and recrystallization, fullerene dimer 118 was obtained in 58%.

**SCHEME 15** Synthesis of dimers 117 and 118 via postmodification

### 7.2 Antimalarial activity

In comparison to artemisinin, post modified fluorinated nonacetal dimer 100a/b (Scheme 12) showed a 2–4-fold decrease in activity, when tested in vitro on chloroquine sensitive NF-54 strain of *P. falciparum* with activities of 28 and 15 nM, respectively. However, their nonfluorinated precursors 5a–a" exhibited superior antimalarial activity, 2–5 times more potent than artemisinin clearly indicating the negative effects of incorporating fluorine into the scaffold. Among the bis benzyl alcohol dimers 103–104, tested in vitro, the compound 103 (Figure 9) displayed the
highest activity against *P. falciparum* (NF54, IC$_{50}$ = 0.77 nM), whereas the corresponding cyclic phosphate ester dimers 104/105 were less active. The highly water-soluble phthalic acid dimer 102 was least active with a 460-fold decrease in activity, clearly indicating the importance of having an adequate hydrophobicity on the dimer scaffold to retain optimal antimalarial activity. Encouraged by the in vitro results, the dimethylphthalate dimer 101 and bis-benzyl alcohol dimer 103 (Figure 9) were tested in vivo through oral (po, 3.10 mg/kg) or subcutaneous (sc, 30.0 mg/kg) administration. Both these dimers exhibited high level of activity with ED$_{50}$ values of 0.06 mg/kg (sc) and 2.6 mg/kg (po), superior to the clinically used antimalarial drug sodium artesunate. Besides their activity, they are completely devoid of toxicity. Dimers bearing vicinal diols, oxime, sulfated esters, epoxide, succinic acid moieties 106a/b, 107, and 108a–c (Figure 9) were tested in vitro against D6 and W2 clones of *P. falciparum*. The dimers displayed activity in nano molar range (1.4–45.5 nM), with compound 108b bearing a succinic acid side chain showed sevenfold higher activity than artesinin and was 354 times more active than chloroquine. However, due to high hydrophilicity, this compound was less active than its alcohol precursor 15c. Artemisinin dimers with a five-carbon spacer bearing benzoate esters (109a–c) (Scheme 14) were tested in vivo with a single dose of 7.1 mg/kg compound on *P. berghei* infected mice along with artemether and/or mefloquine hydrochloride, taken alone or in combination. All the benzoate ester dimers displayed clearance of the parasitemia (>99.5%) in 3 days post administration, similar to artemether. All compounds were devoid of toxicity. Posner et al. studied the survival time of mice infected with *P. berghei*, after treatment with two carbon linked artemisinin dimers 112a–f and 116a–e (oxime), 115a–n (alcohol/
carbamate) and 114a–o (carbonate and thiocarbonate) in combination with clinical drug mefloquine, artemether and also lumifantidine (oxime ether dimers). Some of these dimers and clinically used drug combinations proved to be excellent, with survival times ranging from 20 to 40 days. Observed survival time of 41 days in case of compound 112c/116a, surpassed all the reference drug combinations and derived SAR revealed that the substitution at position 3 significantly influenced the antimalarial activity of the compounds.

7.3 | Anticancer activity

Posner's group examined the antiproliferative activity of fluorinated nonacetal dimer 100a/b on murine keratinocytes and the derived IC50 > 15 nM, which were far less cytotoxic than their nonfluorinated counterparts (dimer 2c–c', IC50 < 4 nM). Trioxane phthalate dimer 101 displayed more than 10-fold the cytotoxicity than the monomeric trioxane dihydroartemisinin (IC50 = 500 nM, HeLa). The diol dimer 103 exhibited even higher cytotoxicity with a 110-fold improvement on HeLa cells (IC50 = 46.5 nM) compared to dihydroartemisinin (Figure 9). Succinyl dimer 108b and oxime dimer 108a displayed 1000-fold higher cytotoxicity than the reference compound artemisinin, when tested against a panel of human cancer cell lines viz., HL-60, LOX IMVI, OVCAR-3, K562, M14, DU145, SKOV3, PC3, A498, Caki, MCF-7, and T-47D (Figure 9). Compound 108a was most active (IC50 = 0.02 µM against prostate PC3).57,62,98 Based on the hallow fiber assay on 12 cancer cell lines compound 108b was chosen for in vivo experiments by Elsolyh's group for in vivo studies on subcutaneous xenograft model of human leukemia cell line HL-60. The compound was found to be active with optimal T/C < 40%.58 This study established the importance of hydrophilicity derived from succinyl moiety, which significantly influence the anticancer potential of dimers. Sulfur linked dimers 117a/b were tested by Jung et al. on five cancer cell lines viz., P388, EL4, Bewo, HT-29, MCF-7. Compound 117a (Figure 9) displayed equal cytotoxicity on EL4 cells as doxorubicin with an IC50 value of 0.04 µM against MCF-7 cell line, clearly proving the effectiveness of shorter chain length in dimers.68 However, the compound was found to be toxic as revealed by its CAM assay as most of the chicken embryos died. Surprisingly, despite its high molecular weight (>1400) and bulkiness, fullerene dimer 118 (Scheme 15) presented 50% inhibitory effect on CAM angiogenesis experiment, equal to (−)fumagillin (57%) and (−)thalidomide (50%).64

8 | CONCLUSIONS

The past two decades witnessed considerable progress in the area of dimerization of artemisinin derivatives as a promising future tool, which has already found applications in the development of new effective anticancer and antimalarial leads. Particularly, many of the artemisinin dimers described in this review are highly efficacious even when administered orally for the treatment of malaria. In general, the chemistry used for the design of artemisinin dimers is straightforward, employing general protocols for linkage of the monomers with the appropriately designed spacer arms or a direct conjugation of the two similar or different monomeric artemisinin moieties. Both cleavable and noncleavable linkers have been employed for the design of dimers. Linker architecture has been found to play a very significant role in the modulation of activity of dimeric drugs in general and in particular for artemisinin dimeric hybrids. The development of a broad variety of linkers, both symmetric and nonsymmetric, led to the clue that linkers not only act as spacers to enable effective interaction of individual artemisinin moieties of the dimer with the biological targets, but also profoundly influence the pharmacokinetic and pharmacodynamic parameters, which has a bearing on the overall efficacy and toxicity of the drug candidates. Extensive research has been carried out to modify the artemisinin moiety to facilitate ligation at the C-10. Some studies have indicated that the stereochemistry at the C-10 position of artemisinin derivatives play significant roles in dimer activity apart from the length and flexibility of the spacer arm. However, a big potential scope of attachment points of linkers to other positions on the artemisinin scaffold was developed for novel dimers, possibly improving their biological activity. The knowledge gained through the design of artemisinin dimers containing host of
structural entities including quinolines, coumarin, fullerene, pyridine, thymoquinone etc. introduced through post-modification of dimers paved new avenues for the incorporation of various other functional entities into the dimer scaffold as protein modulators to further improve the efficacy and alleviate toxicity.

Despite tremendous progress achieved in the past two decades on the development of novel artemisinin dimers as therapeutics for malaria or certain forms of cancer, challenges such as the understanding of the SAR of the conjugate with regard to linker architecture and ensuing pharmaco-kinetic/-dynamic properties of the dimer as well as its impact on the overall pharmacological and toxicological activity of the conjugate are to be addressed. Studies regarding the optimal length and confirmation mobility of spacer arm vis-à-vis the drug targets in the intracellular space must be clearly understood. This understanding becomes more relevant in case of dimers with noncleavable linker, as the overall success of such conjugates depend on the proper understanding of the optimal length of spacer arm to enable effective binding of the artemisinin ligands with the cognate biological targets. Other important attributes like the effect on drug resistance, therapeutic window, shelf life and formulation challenges, should be studied to understand the suitability of artemisinin dimers for their clinical applications even though a molecular weight of artemisinin dimers is higher than 500 daltons and this is not compliant with Lipinski Rule of 5. As with many other rules of thumb, there are also exceptions. Notably, Lipinski specifically states that the Rule of 5 only holds for compounds that are not substrates for active transporters. When the Rule of 5 was developed in 1997, information about drug transporters was very limited. Most probably, however, almost all drugs are substrates for some transporter. Studies to date have not been able to show this for artemisinin dimers because biologists and chemists (among them our group and collaborators) just begin to gain the knowledge and tools that allow investigation of artemisinin dimers and hybrids for uptake transporters. Moreover, the “Lipinski rule of 5” has been formulated based on a distribution of calculated properties among several thousand drugs. Several clinically used anticancer and antimicrobial drugs apart from vitamins and cardiovascular drugs fall outside the parameter cutoffs in the rule. Structural features of these compounds make them substrates for naturally occurring transporters of the cell and presumably, the artemisinin dimers fall under this category.

Given the fact that the mechanistic studies pertaining improved efficacy of the artemisinin hybrids are poorly understood so far, the latest developments in this area, like the work on target fishing by UV cleavable polymer bound artemisinin oligomers through mass spectroscopy, should pave the way for the identification of cognate biological targets for various artemisinin conjugates, which in turn help us to understand the mechanism of their enhanced efficacy. As summarized in this review, artemisinin dimers often exhibited superior efficacy with reduced toxicity compared to monotherapy, further design of novel artemisinin dimers offers a promising approach for the discovery of new drug candidates, as a better and safer alternative to some of the existing anti-infective and anticancer drugs.

ACKNOWLEDGMENTS
We gratefully acknowledge the financial support from Deutsche Forschungsgemeinschaft (DFG) by grant TS 87/16-3. Generous support by the Alexander von Humboldt (AvH) foundation (Fellowship for a Renewed Research Stay in Germany from AvH to H.M.S.K.) is gratefully acknowledged. We also thank the Interdisciplinary Center for Molecular Materials (ICMM), the Graduate School Molecular Science (GSMS) for research support, as well as Emerging Fields Initiative (EFI) "Chemistry in Live Cells" supported by Friedrich-Alexander-Universität Erlangen-Nürnberg for funding. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
Design: Aysun Çapçı and Svetlana B. Tsogoeva. Writing—original draft preparation: Aysun Çapçı and Tony Fröhlich. Writing—review and editing: Aysun Çapçı, Lars Herrmann, Halmuthur M. Sampath Kumar, Tony Fröhlich, and Svetlana B. Tsogoeva. Editing: Aysun Çapçı, Lars Herrmann, and Svetlana B. Tsogoeva. All authors have read and agreed to the published version of the manuscript.
REFERENCES

1. Tu Y. The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. Nat Med. 2011;17:1217-1220.
2. Qinghaosu Antimalarial Coordinating Research Group. Antimalaria studies on Qinghaosu. Chin Med J. 1979;92(12):811-816.
3. Klayman DL. Qinghaosu (artemisinin): an antimalarial drug from China. Science. 1985;228(4703):1049-1055.
4. Price RN. Artemisinin drugs: novel antimalarial agents. Expert Opin Investig Drugs. 2000;9(8):1815-1827.
5. Haynes RK. Artemisinin and derivatives: the future for malaria treatment? Curr Opin Infect Dis. 2001;14(6):719-726.
6. Haynes RK, Fugmann B, Stetter J, et al. Artemisone—a highly active antimalarial drug of the artemisinin class. Angew Chem Int Ed. 2006;45(13):2082-2088.
7. Haynes RK, Ho WY, Chan HW, et al. Highly antimalaria-active artemisinin derivatives: biological activity does not correlate with chemical reactivity. Angew Chem Int Ed. 2004;43(11):1381-1385.
8. Guo J, Guiguemde AW, Bentura-Marciano A, et al. Synthesis of artemiside and its effects in combination with conventional drugs against severe murine malaria. Antimicrob Agents Chemother. 2012;56(1):163-173.
9. Brossi A, Venugopalan B, Dominguez Gerpe L, et al. Arteether, a new antimalarial drug: synthesis and antimalarial properties. J Med Chem. 1988;31(3):645-650.
10. Wang J, Zhang CJ, Chia WN, et al. Haem—activated promiscuous targeting of artemisinin in Plasmodium falciparum. Nat Commun. 2015;6:10111-10122.
11. Wang J, Zhang J, Shi Y, et al. Mechanistic investigation of the specific anticancer property of artemisinin and its combination with aminolevulinic acid for enhanced anticolorectal cancer activity. ACS Cent Sci. 2017;3(7):743-750.
12. World Health Organization. Guidelines for the treatment of malaria. 2015.
13. Tietze LF, Bell HP, Chandrasekhar S. Natural product hybrids as new leads for drug discovery. Curr Opin Biotechnol. 2004;15(6):584-590.
14. Mehta G, Singh V. Hybrid systems through natural product leads: an approach towards new molecular entities. Chem Soc Rev. 2002;31(6):324-334.
15. Ganesan A. Natural products as a hunting ground for combinatorial chemistry. Curr Opin Biotechnol. 2004;15(6):590-602.
16. Jung M, Lee K, Kim H, Park M. Recent advances in artemisinin and its derivatives as antimalarial and antitumor agents. Curr Med Chem. 2004;11(10):1265-1284.
17. Gademann K. Natural product hybrids. Chimia. 2006;60(12):841-845.
18. Meunier B. Hybrid molecules with a dual mode of action: dream or reality? Acc Chem Res. 2008;41(1):69-77.
19. Tsogoeva SB. Recent progress in the development of synthetic hybrids of natural or unnatural bioactive compounds for medicinal chemistry. Mini-Rev Med Chem. 2010;10(9):773-793.
20. Chaturvedi D, Goswami A, Saikia PP, Barua NC, Rao PG. Artemisinin and its derivatives: a novel class of antimalarial and anti-cancer agents. Chem Soc Rev. 2010;39(2):435-454.
21. Reiter C, Capci Karagöz A, Fröhlich T, et al. Synthesis and study of cytotoxic activity of 1,2,4-trioxane- and egonol-derived molecules against Plasmodium falciparum and multidrug-resistant human leukemia cells. Eur J Med Chem. 2014;75:403-412.
22. Hutterer C, Niemann I, Milbradt J, et al. The broad-spectrum antifungal drug artemisunate interferes with the canonical nuclear factor kappa B (NF-xB) pathway by targeting RelA/p65. Antiviral Res. 2015;124:101-109.
23. Reiter C, Fröhlich T, Gruber L, et al. Highly potent artemisinin-derived dimers and trimers: synthesis and evaluation of their antimalarial, antileukemia and antiviral activities. Bioorg Med Chem. 2015;23(17):5452-5458.
24. Bock CM, Parameshwarappa G, Bönsch S, et al. Generation of complex azabicycles and carbobicycles from two simple compounds in a single operation through a metal-free six-step domino reaction. Chem Eur J. 2016;22(15):5189-5197.
25. Ackermann A, Karagöz AC, Choochani A, et al. Cytotoxic profiling of artesunic and betulinic acids and their synthetic hybrid compound on neurons and gliomas. Oncotarget. 2017;8(37):61457-61474.
26. Fröhlich T, Ndreshkjana B, Muenzner JK, et al. Synthesis of novel hybrids of thymoquinone and artemisinin with high activity and selectivity against colon cancer. Chem Med Chem. 2017;12(3):226-234.
27. Fröhlich T, Reiter C, Ibrahim MM, et al. Synthesis of novel hybrids of quinazoline and artemisinin with high activities against Plasmodium falciparum, human cytomegalovirus, and leukemia cells. ACS Omega. 2017;2(6):2422-2431.
28. Held FE, Guryev AA, Fröhlich T, et al. Facile access to potent antiviral quinazoline heterocycles with fluorescence properties via merging metal-free domino reactions. Nat Commun. 2017;8:15071-15080.
29. Fröhlich T, Reiter C, Saeed MEM, et al. Synthesis of thymoquinone-artemisinin hybrids: new potent antileukemia, antiviral, and antimalarial agents. ACS Med Chem Lett. 2018;9(6):534-539.
30. Haynes RK, Chan HW, Cheung MK, et al. C-10 ester and ether derivatives of dihydroartemisinin-10-α artesunate, preparation of authentic 10-β artesunate, and of other ester and ether derivatives bearing potential aromatic intercalating groups at C-10. Eur J Org Chem. 2002;2002(1):113-132.

31. Walsh JJ, Coughlan D, Heneghan N, Gaynor C, Bell A. A novel artemisinin-quinine hybrid with potent antimalarial activity. Bioorg Med Chem. 2007;17(13):3599-3602.

32. Njogu PM, Gut J, Rosenthal PJ, Chibale K. Design, synthesis, and antiplasmodial activity of hybrid compounds based on (2R,3S)-N-benzoyl-3-phenylisoserine. ACS Med Chem Lett. 2013;4(7):637-641.

33. Le TN, De Borggraeve WM, Grellier P, Pham VC, Dehaen W, Nguyen VH. Synthesis of 11-aza-artemisinin derivatives using the Ugi reaction and an evaluation of their antimalarial activity. Tetrahedron Lett. 2014;55(35):4892-4894.

34. Wang N, Wicht KJ, Shaban E, et al. Synthesis and evaluation of artesunate–indoloquinoline hybrids as antimalarial drug candidates. MedChemComm. 2014;5(7):927-931.

35. Mariani A, Mai TT, Zacharioudakis E, et al. Iron-dependent lysosomal dysfunction mediated by a natural product hybrid. Chem Commun. 2016;52(7):1358-1360.

36. Jana S, Iram S, Thomas J, Hayat MQ, Pannecouque C, Dehaen W. Application of the triazolization reaction to afford dihydroartemisinin derivatives with anti-HIV activity. Molecules. 2017;22(2):303-316.

37. Jeyadevan JP, Bray PG, Chadwick J, et al. Antimalarial and antitumor evaluation of novel C-10 non-acetal trioxane dimers in prostate cancer cell lines. Eur J Med Chem. 2017;133:610-616.

38. Posner GH, Paik IH, Sur S, et al. Orally active, antimalarial, artemisinin hybrid. J Med Chem. 2003;46(6):1060-1065.

39. Posner GH, Ploypradith P, Parker MH, et al. Antimalarial, antiproliferative, and antitumor activities of artemisinin-derived, chemically robust, trioxane dimers. J Med Chem. 1999;42(21):4275-4280.

40. Posner GH, Paik IH, Sur S, et al. Orally active, antimalarial, anticancer, artemisinin-derived trioxane dimers with high stability and efficacy. J Med Chem. 2003;46(6):1060-1065.

41. Chen HW, Cheung MK, et al. Artemisinin dimer anticancer activity correlates with heme oxygen species generation and endoplasmic reticulum stress induction. Int J Cancer. 2009;125(6):1266-1275.
58. Posner GH, Northrop J, Paik I-H, et al. New chemical and biological aspects of artemisinin-derived trioxane dimers. *Bioorg Med Chem*. 2002;10(1):227-232.
59. Posner GH, Ploypradith P, Hapangama W, et al. Trioxane dimers have potent antimalarial, antiproliferative and antitumor activities in vitro. *Bioorg Med Chem*. 1997;5(7):1257-1265.
60. Moon DK, Tripathi A, Sullivan D, Siegler MA, Parkin S, Posner GH. A single, low, oral dose of a 5-carbon-linked trioxane dimer orthoester plus mefloquine cures malaria-infected mice. *Bioorg Med Chem Lett*. 2011;21(9):2773-2775.
61. Jung M, Yu D, Bustos D, Elssohy MN, Mcchesney JD. A concise synthesis of 12-(3’-hydroxy-N-propyl)-deoxoartemisinin. *Bioorg Med Chem Lett*. 1999;1(12):741-744.
62. Slade D, Galal AM, Gul W, et al. Antiprototrocal, anticancer and antimicrobial activities of dihydroartemisinin acetate dimers and monomers. *Bioorg Med Chem*. 2009;17(23):7949-7957.
63. Lombard MC, N'Da DD, Breytenbach JC, Smith PJ, Lategan CA. Artemisinin–quinoline hybrid-dimers: synthesis and in vitro antiplasmodial activity. *Bioorg Med Chem Lett*. 2010;20(23):6975-6977.
64. Jung M, Tak J, Chung WY, Park KK. Antiangiogenic activity of deoxoartemisinin derivatives on chorioallantoic membrane. *Bioorg Med Chem Lett*. 2006;16(5):1227-1230.
65. Jung M, Park N, Moon HI, Lee Y, Chung WY, Park KK. Synthesis and antitumor activity of novel amide derivatives of non-acetal deoxoartemisinin. *Bioorg Med Chem Lett*. 2009;19(22):6303-6306.
66. Saikia B, Saikia PP, Goswami A, Barua NC, Saxena AK, Suri N. Synthesis of a novel series of 1,2,3-triazole-containing artemisinin dimers with potent antitumor activity involving huisgen 1,3-dipolar cycloaddition reaction. *Synthesis*. 2011;19(19):3173-3179.
67. Buragohain P, Saikia B, Surineni N, Barua NC, Saxena AK, Suri N. Synthesis of a novel series of artesinin dimers with potent antitumor activity involving Sonogashira cross-coupling reaction. *Bioorg Med Chem Lett*. 2014;24(1):237-239.
68. Jung M, Lee S, Ham J, Lee K, Kim H, Kim SK. Antitumor Activity of Novel Deoxoartemisinin Monomers, Dimers, and Trimer. *J Med Chem*. 2003;46(6):987-994.
69. Reiter C, Fröhlich T, Zeino M, et al. New efficient artemisinin derived agents against human leukemia cells, human cytomegalovirus and Plasmodium falciparum: 2nd generation 1,2,4-triazole-ferrocene hybrids. *Eur J Med Chem*. 2015;97:164-172.
70. Magoulas GE, Tsigkou T, Skondra L, et al. Synthesis of novel artemisinin dimers with polyamine linkers and evaluation of their potential as anticancer agents. *Bioorg Med Chem*. 2017;25(14):3756-3767.
71. Pearce AN, Kaiser M, Copp BR. Synthesis and antimalarial evaluation of artesunate-polyamine and trioxolane-polyamine conjugates. *Eur J Med Chem*. 2017;140:595-603.
72. Fröhlich T, Hahn F, Belmudes L, et al. Synthesis of artemisinin-derived dimers, trimers and dendrimers: investigation of their antimalarial and antiviral activities including putative mechanisms of action. *Eur J Chem*. 2018;24(32):8103-8113.
73. Çapçi Karagöz A, Reiter C, Seo E-J, et al. Access to new highly potent antileukemia, antiviral and antimalarial agents via hybridization of natural products (home)egonol, thymoquinone and artemisinin. *Bioorg Med Chem*. 2018;26(12):3610-3618.
74. Wu Y, Parapini S, Williams I, et al. Facile preparation of N-glycosylated 10-piperazinyl artemisinin derivatives and evaluation of their antimalarial and cytotoxic activities. *Molecules*. 2018;23(7):1713-1731.
75. Lombard MC, N’Da DD, Breytenbach JC, et al. Antimalarial and anticancer activities of artemisinin–quinoline hybrid-dimers and pharmacokinetic properties in mice. *Eur J Pharm Sci*. 2012;47(5):834-841.
76. Gaur R, Pathania AS, Malik FA, Bhakuni RS, Verma RK. Synthesis of a series of novel dihydroartemisinin monomers and dimers containing chalcone as a linker and their anticancer activity. *Eur J Med Chem*. 2016;122:232-246.
77. Cloete TT, de Kock C, Smith PJ, N’Da DD. Synthesis, in vitro antiplasmodial activity and cytotoxicity of a series of artemisinin-triazine hybrids and hybrid-dimers. *Eur J Med Chem*. 2014;76:470-481.
78. Beekman AC, Barentsen AR, Woerdenbag HJ, et al. Stereochemistry-dependent cytotoxicity of some artemisinin derivatives. *J Nat Prod*. 1997;60(4):325-330.
79. Beekman AC, Wierenga PK, Woerdenbag HJ, et al. Artemisinin-derived sesquiterpene lactones as potential anti-tumour compounds: cytotoxic action against bone marrow and tumour cells. *Planta Med*. 1998;64(7):615-619.
80. Phothongkam S, Chancharunee S, Saovapakhiran A, Wichai U, Pohmakotr M. Facile synthesis and anticancer activity of C-10 non-acetal deoxoartemisinin dimers. *Bioorg Med Chem Lett*. 2012;22(24):7598-7601.
81. Grelléipois F, Crousse B, Bonnet-Delpon D, Bégue JP. Synthesis of new artemisinin-derived dimers by self-cross-metathesis reaction. *Org Lett*. 2005;7(23):5219-5222.
82. Xie L, Zhao Y, Zhai X, et al. The application of tandem Aza-Wittig reaction to synthesize artemisinin–guanidine hybrids and their anti-tumor activity. *Arch Pharm*. 2011;344(10):631-638.
83. Mott BT, Tripathi A, Siegler MA, Moore CD, Sullivan DJ, Posner GH. Synthesis and antimalarial efficacy of two carbon-linked, artemisinin-derived trioxane dimers in combination with known antimalarial drugs. *J Med Chem*. 2013;56(6):2630-2641.
84. Kien VT, Binh LH, Phong PH, et al. Novel artemisinin-derived dimers: synthesis and evaluation of anti-cancer activities. *Lett Drug Des Discov*. 2017;14(1):102-111.
AUTHOR BIOGRAPHIES

Aysun Çapcı received her BSc and MSc degrees in Chemistry from the Ege University (Turkey). In 2019, she successfully completed her doctoral studies under the supervision of Prof. S. B. Tsogoeva at Friedrich-Alexander University of Erlangen-Nürnberg, Germany, supported by a Fellowship from the German Academic Exchange Service DAAD. She was one of the recipient of Renate-Wittern-Sterzel-Gleichstellungspreis for Equality in the field of gender and diversity in 2019. Her research is focused on the organocatalytic click reactions and development of novel natural product hybrids as potent antimalarial and anticancer therapeutics.

Lars Herrmann received his BSc and MSc degrees in Chemistry from the Friedrich-Alexander University Erlangen Nürnberg (Germany). In 2019, he began his doctoral studies under the supervision of Prof. S. B. Tsogoeva at Friedrich-Alexander University of Erlangen-Nürnberg. Since 2019 he is a member of the Graduate School Molecular Science (GSMS) of the Friedrich-Alexander University of Erlangen-Nürnberg. His research is...
focused on the development of novel natural product hybrids via organocatalytic click reactions as potent antimalarial, antiviral and anticancer therapeutics.

Halmuthur M. Sampath Kumar obtained his MSc in organic chemistry from Gulbarga University and a PhD degree from the Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad, in the area of biomimetic chemistry. In 2000, he moved to the Max Planck Institute for Molecular Physiology at Dortmund (Germany) as Alexander von Humboldt Fellow to work with Prof. Dr. Dr.(h.c.) Herbert Waldmann in the area of nuclear localization and gene therapy. After returning to India in 2002, he continued his research work at CSIR-IICT on agrochemical and pharmaceutical technology development. He relocated to the CSIR-Regional Research Laboratory in 2004, presently rechristened as CSIR-IIIM, where he instituted a new department dedicated to biological chemistry research and served as the chairman of the department till 2009. Currently, he is the project coordinator and nodal scientist for the vaccine immunology programme at CSIR-IICT. Focus of his current research is on the development of novel small molecule immunomodulators based on natural product scaffolds, vaccine(Th1) adjuvants/mucosal delivery systems, peptide epitope based wholly synthetic vaccines and pharmaceutical hybrids.

Tony Fröhlich was born in Fürth (Germany) in 1989. He received his MSc degree in Molecular Science from the University of Erlangen-Nuremberg in 2013. The same year he began his graduate studies under the supervision of Prof. S. B. Tsogoeva on the research topic of artemisinin-based hybrids and oligomers. He obtained his PhD degree in chemistry at the University of Erlangen-Nuremberg in 2019. Currently, he is working as a postdoctoral researcher at the Helmholtz Center Munich (HMGU) on small molecule inhibitors of PEX14 as potential drug candidates for Chagas disease and African sleeping sickness.

Svetlana B. Tsogoeva studied chemistry at St. Petersburg State University (Russia), where she completed her doctoral thesis in 1998 on the “Synthesis of Modified Analogues of Steroid Estrogens” supported by Procter & Gamble. In 1998, she moved to the Johann Wolfgang Goethe-University, Frankfurt am Main (Germany) for a postdoctoral research. In July 2000, she joined the Degussa AG Fine Chemicals Division as a research scientist, where she has been working on the development of new oligopeptide catalysts for the enantioselective Julia-Colonna asymmetric epoxidation of olefins. In January 2002, she was appointed a first junior professor in Germany at the Georg-August-University of Göttingen, where she established her own research group supported by BMBF, DFG, FCI and Degussa AG. Since February 2007 she holds the position of Professor of Organic Chemistry at the Department of Chemistry and Pharmacy of the Friedrich-Alexander University of Erlangen-Nürnberg, Germany. Her research is currently focused on asymmetric organocatalysis, one-pot and domino processes, deracemization of chiral bioactive compounds, synthesis of artemisinin-derived hybrids for medicinal chemistry, as well as chemistry in live cells.

SUPPORTING INFORMATION
Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Çapçı A, Herrmann L, Sampath Kumar HM, Fröhlich T, Tsogoeva SB. Artemisinin-derived dimers from a chemical perspective. Med Res Rev. 2021;41:2927–2970.
https://doi.org/10.1002/med.21814