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Bis(benzofuran–thiazolidinone)s and Bis(benzofuran–thiazinanone)s as Inhibiting Agents for Chikungunya Virus

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Keywords

Chikungunya virus, Benzofuran, Thiazolidinone, Thiazinanone, Suramin, Anti-viral

ABSTRACT

There are currently still no approved antiviral drugs to treat or prevent chikungunya virus (CHIKV) infections despite the fact that this arbovirus continues to cause outbreaks in Africa, Asia, and South- and Central-America. Thus 20 new conjugated compounds in the families of bis(benzofuran–1,3-thiazolidin-4-one)s and bis(benzofuran–1,3-thiazinan-4-one)s were designed based on the structural features of suramin. These new compounds were synthesized by chemical methods and their structures were confirmed spectroscopically. In CPE reduction assays, six of these new bis-conjugates inhibited CHIKV replication in Vero E6 cells with EC_{50} in the range of 1.9 to 2.7 μM and selectivity index values of ~75 or higher. These results and compounds provide a starting point for further optimization, design, and synthesis of new antiviral agents for this (re)emerging disease.

1. Introduction

Chikungunya virus (CHIKV) is an arthrogenic alphavirus, which has infected millions of people since its re-emergence in 2005, when it caused large outbreaks in Asia and Africa. In 2013, CHIKV emerged in the Caribbean (Weaver, 2014; Weaver and Lecuit, 2015) and started another massive outbreak, which has thus far resulted in >1.2 million cases in the Americas alone. At the moment there are no approved vaccines or specific antiviral drugs to prevent or treat chikungunya disease (Hwu et al., 2017). Several molecules with inhibitory effects on CHIKV in cell culture, and in some cases in animal/mouse models, have been reported (Kuo et al. 2016), but none of them has advanced into clinical trials (Abdelnabi et al. 2017).

Our laboratories have previously developed several new compounds with activity against CHIKV (Hwu et al., 2015; Albulescu et al., 2015). The first class of these compounds consists of uracil–coumarin–arene conjugates and the second class concerns

suramin (**1**) and its derivatives. Suramin inhibits CHIKV replication through multiple mechanisms (Kuo et al. 2016; Albulescu et al., 2015), mainly by interfering with an early step of the replication cycle, but with (minor) additional effects on later steps, like RNA synthesis. Recently, suramin has also been reported to inhibit Zika virus replication by interfering with virus attachment and release of infectious particles (Albulescu et al. 2017).

Suramin is a symmetric molecule with a urea (NH–CO–NH) group in the center as the "neck", two benzamido moieties as the "shoulder", two methylbenzamido moieties as the "arms", two naphthalene rings as the "palms", and six sulfonate groups as the "fingers". A tetra-sulfonate derivative of suramin that lacks two sulfonate groups is less active against CHIKV compared with suramin (Albulescu et al., 2015), although it inhibits human and murine norovirus RNA-dependent RNA polymerase (RdRp) activity *in vitro* with an IC_{50} of 28 nM (Croci et al., 2014). Of a series of eleven suramin-related analogs that were tested for their ability to inhibit CHIKV RNA synthesis *in vitro* and to inhibit CHIKV replication in cell culture, only three exhibited inhibitory activity. All of these had features very similar to suramin (Albulescu et al., 2015).

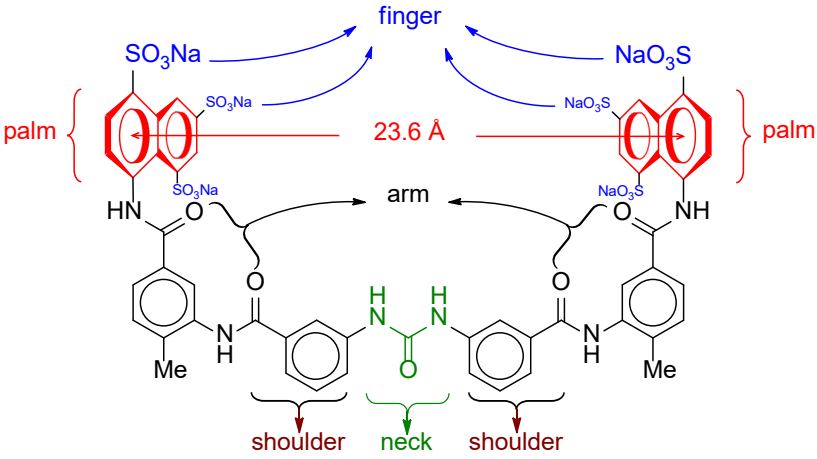
Several other synthetic compounds with a dimeric structure similar to suramin also show significant biological activities. Prominent examples include atracurium besilate (Hughes, 1986), cisatracurium besilate (Bryson and Faulds, 1997), cromoglicic acid (Penumutchu et al., 2014), daclatasvir (Press release, 2015), ombitasvir (Press release, 2014), and pentamidine (Nguewa et al., 2005). Among them, daclatasvir (trade name Daklinza) and ombitasvir (trade names Viekira Pak and Technivie) are antiviral drugs for the treatment of hepatitis C virus infection. The structural "widths" of these two dimeric antiviral compounds are around 22.4 and 24.5 Å, respectively.

Benzofuran is one of the most important oxygen-containing heterocycles (Khanam and Shamsuzzaman, 2015). Many benzofuran derivatives display potent biological and pharmacological properties, such as β-adrenoceptor antagonistic (Narimatsu et al., 2003),

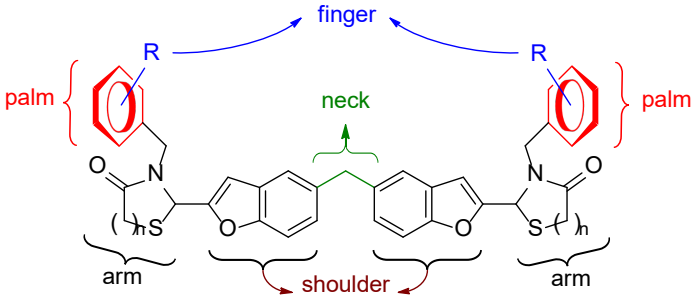
analgesic, anti-arrhythmic (Spaniol et al., 2001), anti-Alzheimer's, anti-dermal, anti-feedantic, anti-hyperglycemic, anti-inflammatory, anti-microbial, anti-pyretic, anti-tumor, immunosuppressive (Cheng et al., 2010; González–Gómez et al., 2005; Khanam and Shamsuzzaman, 2015; Kao and Chern, 2001), and especially antiviral activities (Naik et al., 2015; He et al., 2015). Moreover, the broad and potent activities of 1,3-thiazolidin-4-ones have established these compounds as biologically important scaffolds. Their biological properties include anthelmintic, anti-bacterial, anti-cancer, anti-convulsant, anti-diabetic, anti-fungal, anti-histaminic, anti-hyperlipidemic, anti-inflammatory, anti-proliferative, anti-tubercular, cardiovascular, follicle stimulating hormone receptor agonist, hypnotic (Verma and Saraf, 2008; Tripathi et al., 2014; Gouvea et al., 2016), and anti-viral activities as well (Barreca et al., 2002; Rao et al., 2004; Rawal et al., 2007). Recently, thiazinanone derivatives have been reported with medicinally important roles. These compounds show potent HIV-RT inhibitory, cyclooxygenase (COX-2) inhibitory (Zebardast et al., 2009), anti-dyslipidemic, anti-hyperglycemic, anti-tumor (Kamel et al., 2010), anti-malarial (Rudrapal et al., 2013), and anti-fungal activities (Verma et al., 2010; Qu et al., 2013). Accordingly, using suramin (**1**) as a model, we designed bis(benzofuran–1,3-thiazolidin-4-one) derivatives **2** and bis(benzofuran–1,3-thiazinan-4-one) derivatives **3** as new types of dimeric compounds, of which the antiviral activities were tested. Suramin (**1**) and bis-benzofurans **2** and **3** have a width of ~23.6 Å (between the two naphthalene rings), 22.7 Å, and 21.7 Å (between the two benzene rings), respectively, on the basis of the conformations shown in structures **1**–**3**. Raj and co-workers (Raj et al., 1998) reported that the two naphthalene rings either fold closer to each other with a distance of ~16–20 Å or stretch away from each other at a ~28–30 Å distance. We aimed to use the two new types of dimeric

conjugates to develop leads against CHIKV. In total, 20 new conjugated compounds and one bis-aldehyde intermediate were synthesized, six of which exhibited significant inhibitory

efficacy against CHIKV. The structure–activity relationships of these bis(benzofuran–thiazolidinone)s **2** and bis(benzofuran–thiazinanone)s **3** are discussed.



1 (suramin)



n =

2. 1 (benzofuran–thiazolidinone)
3. 2 (benzofuran–thiazinanone)

2. Materials and methods

A detailed description of the materials and methods is available in the supporting information file.

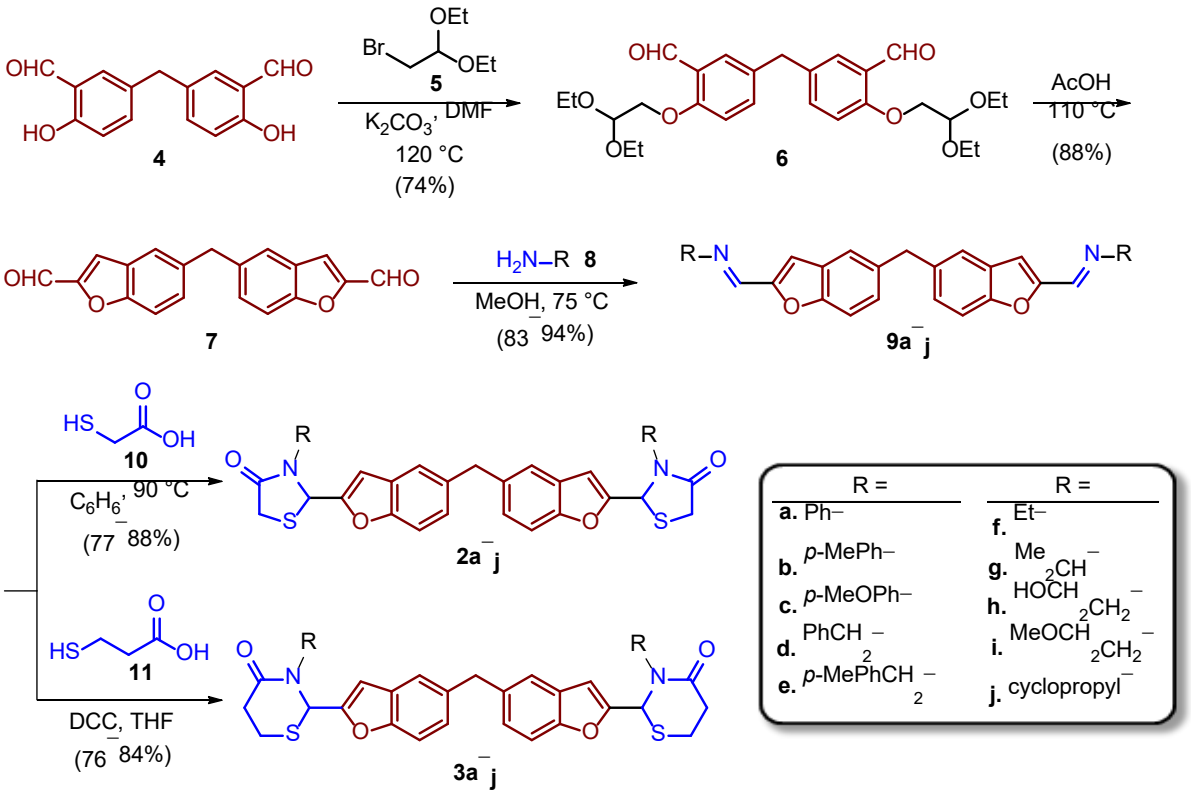
3. Results and discussion

3.1 Synthesis of New Conjugated Dimers and Their Structural Identification (Scheme 1)

The target compounds with the scaffolds of **2** and **3** were obtained from the common intermediate bisbenzofuran-2-al **7**. Its preparation started with coupling bissalicyaldehyde **4** (Delogu et al., 2010) with commercially available bromoacetaldehyde diethyl ether (**5**) in the presence of $K_2CO_{3\,(s)}$ in dry DMF (Scheme 1). After the reaction mixture was heated to 120 °C, it gave the desired diacetal **6**. Using acetic acid as the catalyst and also as the solvent, this diacetal **6** underwent sequential deacetylation, intramolecular aldol condensation, and acid-catalyzed dehydration at 110 °C. The desired benzofuran-2-al dimer **7** was generated in 88% yield and purified as yellow crystals with mp 150.2–151.6 °C. Then alkyl-, cycloalkyl-, aryl-, and aralkylamines **8a**–**j** were used to

condense with bisbenzofuranal **7** in excess in dry methanol to give bisimines **9a**–**j** as solids in 83–94% yields.

Subsequent ring formation through condensation of bisimines **9a**–**j** with 2-mercaptoacetic acid (**10**) in benzene at 90 °C led to the desired targets **2a**–**j** as solids in 77–88% yields. The structures of all these new bis(benzofuran–1,3-thiazolidin-4-one)s were identified on the basis of their spectroscopic characteristics. For example, the exact mass of compound **2g** was measured as 534.1651 for M^+, which is very close to its theoretical value of 534.1647 for the species $(C_{29}H_{30}N_2O_4S_2)^+$. The generation of two thiazolidinone rings is supported by presence of two NCHS protons as a doublet with a long-range coupling with



Scheme 1. Synthetic procedures for generating the targets bis(benzofuran–thiazolidin-4-one)s **2** and bis(benzofuran–thiazinan-4-one)s **3**

only one of the two $SCH_2C=O$ protons to give a J^4 = 1.2 Hz at 5.72 ppm in the ^1H NMR spectrum (Cunico et al. 2006). The two sets of diastereotopic $SCH_2C=O$ protons in the thiazolidinone ring resonated at 4.00 ppm as a double of doublet with a J^2 = 15.2 and J^4 = 1.2 Hz and at 3.53 ppm as a doublet with J^2 = 15.2 Hz. The center of this compound contained a methylene joint, in which the CH_2 resonated at 4.10 ppm. It also exhibited a multiplet at 4.33–4.26 ppm for two protons due to the two $CHMe_2$ groups attached to two separated nitrogen atoms in thiazolidinone rings. The twelve methyl protons of two isopropyl groups showed resonance as a doublet with a J = 6.8 Hz at 1.27 and 0.87 ppm. The NC=O carbon resonated at 171.1 ppm in the ^{13}C NMR spectrum and the amido C=O group exhibited a strong absorption band at 1673 cm^{-1} in the IR spectrum. These observations are consistent with those reported by Srivastava and co-worker (Srivastava et al., 2007).

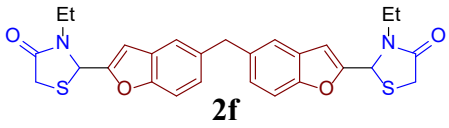
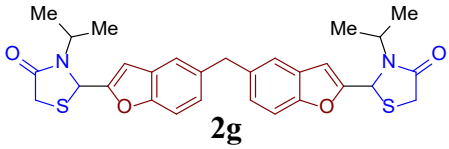
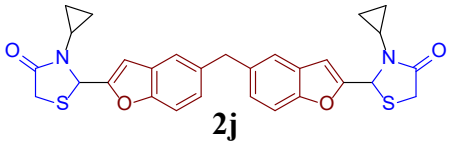
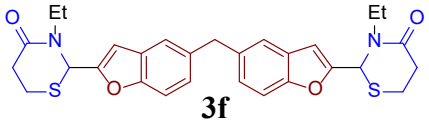
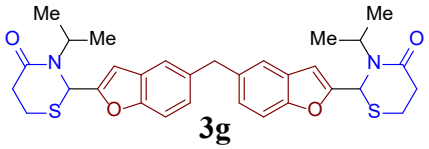
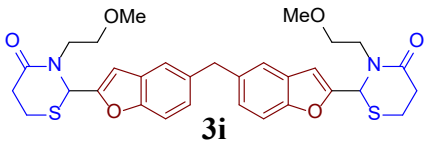
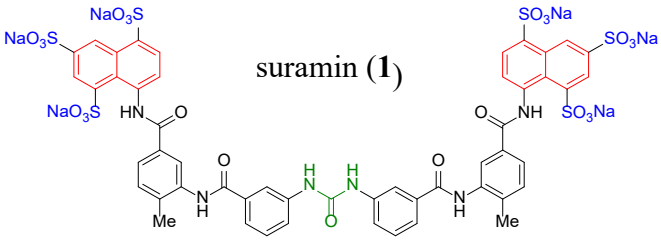
Attempts to synthesize bis(benzofuran–1,3-thiazinan-4-one)s **3** from bisimines **9a**–**j** and 3-mercaptopropionic acid (**11**) using the same cyclization conditions described above (for 2a-j) resulted in low yields (<15%). After many trials, the use of *N,N′*-dicyclohexylcarbodiimide (DCC, 2.5 equiv) as an activating agent (Valeur and Bradley, 2009) in THF led to the conjugated compounds **3a**–**j** as solids in 76–84% yields. For bis(benzofuran–thiazinanone) **3g**, the two NCHS protons of thiazinanone rings showed a singlet at 5.59 ppm in the ^1H NMR spectrum. The four $SCH_2C=O$ protons in the thiazinanone ring resonated as multiplet at 3.07–2.98 and 2.79–2.73 ppm. The NC=O carbon resonated at 169.0 ppm in the ^{13}C NMR spectrum and the amido C=O group in the six-membered rings exhibited a strong absorption band at 1655 cm^{-1} in the IR spectrum.

3.2 Evaluation of Anti-CHIKV Activity

The antiviral activity of bis(benzofuran–1,3-thiazolidin-4-one)s **2** and bis(benzofuran–1,3-thiazinan-4-one)s **3** was first analyzed in cytopathic effect (CPE) reduction assays with CHIKV by testing four different concentrations (i.e., 100, 25, 6.3, and 1.6 μM) in two independent experiments. Only compounds that showed at least 50% protection against CHIKV-induced CPE in this primary screen were selected for validation in a secondary screen. In that case, eight 2-fold serial dilutions of compounds with an initial starting concentration of 200 μM were analyzed (in quadruplicate) to determine the EC_{50}. Cytotoxicity was analyzed in parallel in uninfected cells to determine the CC_{50}. The obtained values were used to determine the selectivity index (SI = CC_{50}/EC_{50}), a measure for the therapeutic window of the compound in the assay system.

Among the 20 new conjugated compounds and one bisaldehyde intermediate **7** shown in Scheme 1, three 1,3-thiazolidin-4-ones (i.e., **2f**, **2g**, and **2j**) and three 1,3-thiazinan-4-ones (i.e., **3f**, **3g**, and **3i)** exhibited limited inhibition of CHIKV replication in Vero E6 cells. Their EC_{50} values ranged from ~1.5 to 2.7 μM (see Table 1) and their selectivity indices ranged from <32 to >100.

Table 1. Inhibition of CHIKV by bis-benzofuran conjugates. EC_{50} values were determined by CPE reduction assays on Vero E6 cells infected with CHIKV LS3. CC_{50} values were determined in parallel and the log P value indicates the lipophilicity of each compound.

bis-conjugate	CC_{50}[a] (μM)	EC_{50}[b] (μM)	SI[c]	log *P*
 **2f**	>200	2.7 ± 1.2	>74.9	4.68
 **2g**	>200	2.0 ± 1.2	>100	4.15
 **2j**	~50	~1.6*	<32.0*	4.56
 **3f**	>200	1.9 ± 1.2	>100	5.52
 **3g**	>200	~1.5*	<133*	5.43
 **3i**	>200	2.3 ± 1.3	>87	4.07
 suramin (**1**)	>800	79 ± 12	>10.1	–3.42

[a]*Cytotoxicity of the compounds in uninfected cells, the concentration of compound that reduced cell viability (measured by MTS assay) to 50% of that of untreated cells.* [b]EC_{50}*, the concentration of compound that resulted in 50% protection from CHIKV-induced*

*cell death (CPE) as determined in CPE reduction assays. [c]Selectivity index. The table lists the average values of two independent experiments, performed in quadruplicate. *Estimate, compounds were toxic and cell viability was only 60-70% viability at concentrations above 3-6 μM. Therefore, full protection (100% viability) was never observed and the concentration that gave half of the maximum effect (~30-35% viability) is reported.* Log *P* values were determined as described in the text and are an average of three independent experiments.

Although the CC_{50} values of compounds **2f**, **2g**, **3f**, **3g**, and **3i** were >200 μM, many other conjugated compounds had clear negative effects on cell viability. Approximately 20-30% reductions in cell viability were observed for several of these compounds starting already at low concentrations. As a result of this toxicity, we did not observe full protection (100% viability) in the CHIKV CPE reduction assays and therefore we could not accurately determine the true EC_{50} value of most of these compounds, but only determine the concentration that gave half of the maximum protective effect (which is indicated with ~ and * in Table 1). We cannot exclude that (part of) the antiviral effect of compounds that adversely affected the host cell metabolism is the result of pleiotropic or non-specific effects on the host cell. However, it should be noted that a high concentration (200 μM) of the most promising compound **2g**, did not lead to serious cytotoxicity, as viability remained 77%.

All of the 20 new compounds **2** and **3** were also screened for antiviral activity against the related Sindbis virus (SINV) and Semliki Forest virus (SFV) in CPE reduction assays. None of the compounds inhibited SINV. While compound **2h** had some inhibitory

effect on Semliki Forest virus, this was likely related to cytotoxicity. Only bis(benzofuran–thiazinanone) **3h** protected cells from SFV-induced CPE with an EC_{50} of 34.8 μM and an SI of >5.74. The fact that none of the compounds that showed some protective effect against CHIKV was active against SINV or SFV suggests that the anti-CHIKV effect is not (only) merely due to nonspecific negative effects on the host cell. Suramin has been reported to interfere with binding of a variety of viruses to their host cells ((Albulescu et al. 2017 and references therein). Therefore, the bis-conjugated compounds that inhibit CHIKV replication in the CPE-based assay might do so by interfering with attachment of the virus to Vero E6 cells, although it cannot be excluded that these molecules (also) inhibit later steps of the replication cycle. Studies to elucidate the exact mode of action of these compounds are currently ongoing.

3.3 Lipophilicity and Potential "Drug-like" Bis-conjugates

The "shake–flask method" (Kraszni et al., 2003) was applied to obtain the molecular lipophilicity (quantified as log *P*) values of bis-conjugated compounds with promising activities in the antiviral assays (Table 1). Thus *n*-octanol and pH 7.4 phosphate buffer were mutually saturated and the phases were separated. Stock solutions of thebis-conjugated compound were prepared in pH 7.4 phosphate buffer and these were partitioned between *n*-octanol and pH 7.4 phosphate buffer. The phase mixtures were shaken for 60 min at constant 25 °C. After separation, the absorbance of the phosphate buffer solutions was measured by UV spectrophotometry. The *P* value corresponds to the quotient of the concentrations of the bis-conjugated derivatives between *n*-octanol and phosphate buffer.

Molecular lipophilicity of chemical entities often plays an important role in the development of drug leads (Hann et al., 2012) and log *P* values between –0.4 and 5.6 are regarded to be in a good range for "drug-like" molecules (Ghose et al., 1999).

Among the new compounds with promising EC_{50} and SI values, the log *P* values of bis-conjugates **2f**, **2g**, **2j**, **3f**, **3g**, and **3i** fell into the range of 4.07–5.52. Therefore, these seven compounds have some potential as "drug-like" candidates for future development.

3.4 Structure–Activity Relationship: Essential Moieties and Substituents

The bis-conjugated compounds with either two five-membered 1,3-thiazolidin-4-one rings or two six-membered 1,3-thiazinan-4-one rings as the "arms" showed comparable EC_{50} for CHIKV and had similar log *P* values (compounds **2f**,**g**,**j** and **3f**,**g**,**i** in Table 1). The substituents attached to the nitrogen atoms played a determining role in the anti-CHIKV activity, as all six active compounds had alkyl substituents as the "palms" such as ethyl, isopropyl, cyclopropyl, and methoxyethyl groups. When the palms were phenyl or benzyl groups with various substituents as the "fingers" in bis-conjugates **2a**–**e** and **3a**–**e** the antiviral activity was lost.

Suramin **1** has anti-CHIKV activity and some of its structural bis-analogs that were designed on the basis of its skeleton also exhibited significant inhibitory activity towards CHIKV (see Table 1). Thus the "urea neck" in suramin can be replaced by a simple "methylene neck" in bis-benzofuran conjugates. Replacement of the benzamido moieties of suramin with benzofuran nuclei in bis-conjugates **2** and **3** as the "shoulders" allowed us to successfully obtain compounds **2f**,**g**,**j** and **3f**,**g**,**i** as anti-CHIKV drug leads. Based on the anti-viral activities of the tested compounds, the six-membered thiazinanone ring could be considered superior to the five-membered thiazolidinone ring. Moreover, the six dimeric

compounds in the family of bis(benzofuran–1,3-thiazolidin-4-one)s and bis(benzofuran–1,3-thiazinan-4-one)s exhibited a ~29 -42 times more potent anti-CHIKV activity than suramin although their toxicity remains an issue to be solved.

4. Conclusions

With the aim to develop small molecules with anti-CHIKV activity, 20 new benzofuran–1,3-thiazolidin-4-one and benzofuran–1,3-thiazinan-4-one conjugated compounds in dimeric form were designed and synthesized. Six of them (i.e., **2f**,**g**,**j** and **3f**,**g**,**i**) inhibited CHIKV replication with EC_{50} values in the range of 1.9–2.7 μM. These compounds had up to 42 times lower EC_{50} values than suramin. However, full protection against CHIKV-induced CPE was not observed due to (limited) cytotoxicity of the compounds at higher concentrations. Further medicinal chemistry efforts are required to reduce the toxicity of the compounds, while retaining or improving their antiviral effect. Nonetheless, these results indicate that the synthesis of the basic skeletons of dimeric benzofuran–1,3-*N*,*S*-heterocycle conjugates provides a new avenue in the development of antiviral leads. The 1,3-*N*,*S*-heterocyclic nuclei could be either a five- or a six-membered ring. The mechanism of action of these new CHIKV inhibitors is currently under investigation.

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Appendix A. Supporting Information.

Supplementary data associated with this article can be found in the online version.

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