Antiviral Agents Towards Chikungunya Virus: Structures, Syntheses, and Isolation from Natural Sources

Jih Ru Hwu, Tapan K. Pradhan, Shwu-Chen Tsay, Mohit Kapoor, Sergey O. Bachurin, Oleg A. Raevsky and Johan Neyts

Abstract Emerging variants of known RNA viruses present an increasing threat to mankind worldwide through their enlarging impact on morbidity and mortality. One of them is the chikungunya disease, which becomes a major public health problem and economic threat. Current world has no approved antiviral drugs available against chikungunya infection. This Book Chapter mainly focuses on discussion of the antiviral compounds that have been reported to inhibit chikungunya virus replication. Various syntheses of antiviral agents, compounds isolated from natural sources, and some structure–activity relationships are illustrated.

Keywords Chikungunya virus · Antivirals · Synthesis · Structure–activity relationship · Mechanism of action

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1 Introduction

Chikungunya virus (CHIKV) is an alphavirus and was first recognized as an epidemic form in East Africa in the early 1950s. Most patients of CHIKV infection suffer from severe persistent arthralgia [1]. Female mosquitoes of the species *Aedes aegypti* and *Aedes albopictus* are mainly responsible for its transmission. The dramatic turn of CHIKV history is its unexpected re-emergence in 2004, which was associated with mutations in the viral genome and a new epidemic strain emerged from the East, Central, South Africa enzootic linage [1, 2]. The outbreaks took place mainly around the Indian Ocean, in particular, the French Island of La Réunion (2005–2006), where about 300,000 cases were confirmed [1, 2]. Since then, thousands of infected travelers imported this virus to many countries of the world. As a result, it is endemic in northern Italy and southern France in 2007. Around the same timeframe, several CHIKV re-emerged incidents happened in Asia, including a local case in Singapore (2008) [3] and hundreds of cases in southern Thailand (2008–2009) [4]. In March 2011, autochthonous transmission of CHIKV was reported in New Caledonia (South Pacific Region), which is also the first report of CHIKV transmission in this region [5]. Another outbreak of autochthonous chikungunya fever with more than 10 cases occurred in Montpellier, France in October 2014 [6]. Beginning in late 2013, the virus started to spread to the Caribbean and into Central and South America, affecting people from 41 countries or more [7, 8]. According to the data of the Pan American Health Organization, about 1.3 million suspected and confirmed cases were reported in these regions by March 2015 [7]. Many factors like commercial transportation, urbanization, deforestation, climate change, have inadvertently formed environments, which brought emerging RNA virus pathogens increasing at an accelerating rate.

In 2008, chikungunya fever is listed as a category C priority pathogen by The U.S. National Institute of Allergy and Infectious Diseases [9]. Considering the global need of new antiviral therapeutics and responding to the health theme of European Union the 7th Framework Call, the Small-molecule Inhibitor Leads Versus Emerging and Neglected RNA Viruses (SILVER) project was conceived in 2010. The SILVER project, led by E. A. Gould and J.-L. Romette, include 24 international research teams and scientists from 12 countries of Europe and Asia. Furthermore, the "Global Virus Network" was initiated in 2011 to identify research gaps and opportunities, including models of infection and disease, epidemiology, candidate vaccines, vector control measures, and antivirals [7].

After being transmitted to the body, CHIKV circulates to the liver, muscle, joints, lymphoid tissue, and brain [9]. There are two phases of infections that were reported in the recent epidemic areas. The first is an acute phase, which lasts from a few days to several weeks. The symptoms include high fever, rigors, headache, photophobia, and petechial/maculopapular rash [9]. The second is a chronic phase, which shows symptoms of polyarthralgia. Although its mortality rate is low, the elderly or those with underlying chronic problems are most likely to have severe complications [9]. During the most recent epidemics in India and in Réunion Island,

severe cases have been described involving encephalitis, myelopathy, peripheral neuropathy, myeloneuropathy, and myopathy [10]. Moreover, some cases of multiorgan failure and eye infections have also been reported [11].

The CHIKV belongs to the *Togaviridae* family and consists of a positive-sense single-stranded RNA genome of about 11.8 kb size. This genome has two open reading frames 5′ and 3′ ends. The 5′ end encodes nsP1, nsP2, nsP3, and nsP4 non-structural proteins; the 3′ end encodes the capsid (C), two glycoproteins E1, E2, and two small cleavage products (E3, 6 K) [11]. Keller et al. [12] present a detailed description of the CHIKV life cycle and identify the key viral target proteins for drug design in a perspective article.

At the present time, there is no vaccine against CHIKV infection licensed for human use. Most of the treatments are symptomatic [13]. Even worse is that the current world has no drug available against CHIKV. Four well-informative review articles covering structures and biological data have been published by Keller [12], Kaur and Chu [13], Neyts [14], Bhakat and Soliman [15], and respective co-authors. The former two are in 2013 and the latter two are in 2015. Moreover, recent review articles involving the discussion and analysis of epidemiology, pathogenesis, global virus network, or cellular mechanisms of action were published by Thiberville et al. [1], Weaver and Forrester [2], McSweegan et al. [7], Schwartz and Albert [9], Couderc and Lecuit [16], Singh and Unni [17], Birendra et al. [18], Parashar and Cherian [19], and Lum and Ng [20].

2 Compound Classes, Structures, Biological Activities, and Mechanisms of Action

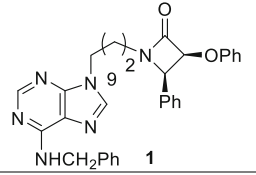
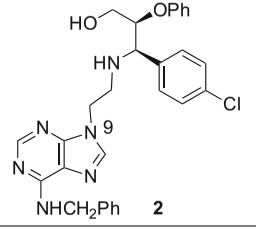
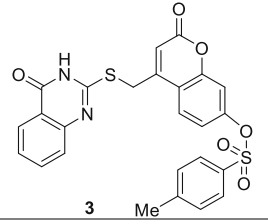
In this review article, we illustrate antiviral agents on the basis of their classes of compounds, structures, synthetic routes, natural sources, biological activities, as well as structure–activity relationship (see Table 1). Emphasis will be placed on the newly developed agents reported after the year of 2013 and syntheses of artificially designed compounds. Efficacy in vivo of most of these compounds, however, has not yet been evaluated in animal models on the basis of the information reported in the original articles.

The established antiviral compounds towards CHIKV can mainly classified into five categories: purines/pyrimidines, nucleosides, alkaloids, terpenoids, and flavaglines. Their characteristics and biological data are illustrated as follows. The table contains information of newly developed antiviral agents reported during the past three years and some established compounds studied earlier for comparison.

A. Purines and Pyrimidines

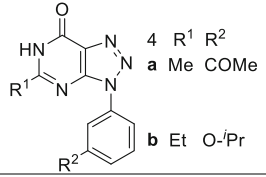
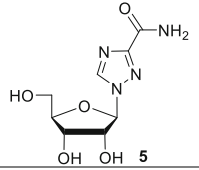
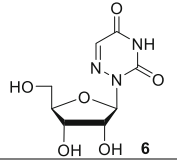
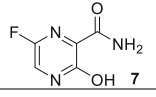
D'hooghe, De Kimpe, and coworkers [21] synthesized a series of purine derivatives, of which antiviral activities were screened against nine different viruses

Table 1 Names, structures, anti-chikungunya virus activities, mechanisms of action, and classes of synthetic and natural compounds

Name (trade name) (year reported)	Structure	Antiviral activities				Mechanism of action
		CC_{50}^{a} (μM)	EC_{50}^{b} (μM)	SI[c]	IC_{50}^{d} (μM)	
Class A. Purine and pyrimidine						
Purine–β-lactam (2012) [21]	 **1**	>98.3	17.1	>5.75	–	Unknown
Purine amino-propanol (2012) [21]	 **2**	71.2	11.5	6.19	–	Unknown
Benouracil–coumarin–arene (2015) [22]	 **3**	117	10.2	11.5	–	Unknown

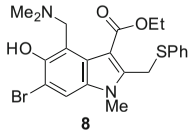
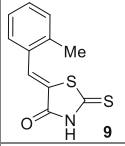
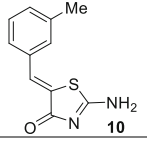
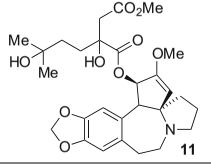
(continued)

Table 1 (continued)

Name (trade name) (year reported)	Structure	Antiviral activities				Mechanism of action
		CC_{50}^{a} (μM)	EC_{50}^{b} (μM)	SI^{c}	IC_{50}^{d} (μM)	
Triazolo-pyrimidine (2014) [23]	 4 R^1 R^2 **a** Me COMe **b** Et O-^{i}Pr	**a**				Unknown
		>743	19	~39.1	–	
		b				
		>668	3	222	–	
Class B. Nucleoside						
Ribavirin (Copegus, Rebetol, Virazole) (2004) [24]	 **5**	30.7 (mM)	341	90.0	–	Inhibition of inosine monophosphate dehydrogenase and depletion of guanosine triphosphate pools
6-azauridine (2004) [24]	 **6**	208	0.82	255	–	Inhibition of orotidine monophosphate decarboxylase and depletion of uridine triphosphate pools
Class C. Alkaloid						
Favipiravir (T-705, Avigan) (2014) [25]	 **7**	>636	25	25.4	–	Inhibition of viral genome replication

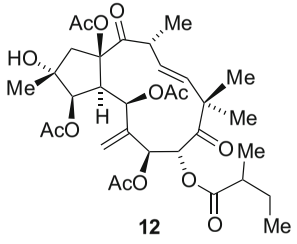
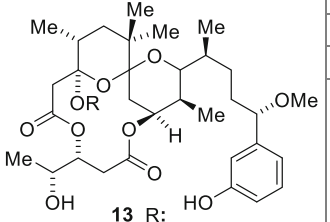
(continued)

Table 1 (continued)

Name (trade name) (year reported)	Structure	Antiviral activities				Mechanism of action
		CC_{50}^{a} (μM)	EC_{50}^{b} (μM)	SI^{c}	IC_{50}^{d} (μM)	
Umifenovir (arbidol) (2011) [26]	 **8**	376	–	–	12.2	Interference with viral entry and alteration of cellular membranes
Thiazolidone (2015) [27]	 **9**	>100	–	–	0.42	Possible inhibition of nsP2 protease
Thiazolidone (2015) [27]	 **10**	>100	–	–	6.8	Possible inhibition of nsP2 protease
Harringtonine (2013) [28]	 **11**	>10	0.24	>41.6	–	Inhibition of replication cycle, affection of RNA production, and interference with viral protein expression

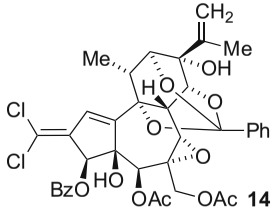
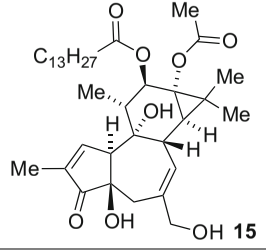
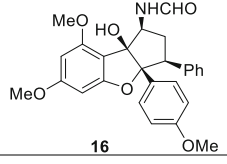
(continued)

Table 1 (continued)

Name (trade name) (year reported)	Structure	Antiviral activities				Mechanism of action
		CC_{50}^{a} (μM)	EC_{50}^{b} (μM)	SI^{c}	IC_{50}^{d} (μM)	
Class D. Terpenoid						
Jatrophane ester (2014) [29]	 **12**	159	0.76	208	–	Unknown
Aplysiatoxin (2014) [30]	 **13** R: **a** H **b** Me	**a**				Unknown
		13.9	1.3	10.9	–	
		b				
		24.8	2.7	9.2	–	

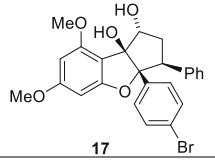
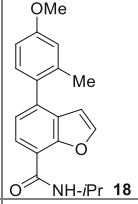
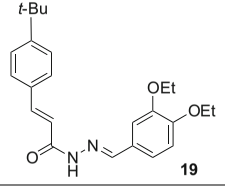
(continued)

Table 1 (continued)

Name (trade name) (year reported)	Structure	Antiviral activities				Mechanism of action
		CC_{50}^{a} (μM)	EC_{50}^{b} (μM)	SI^{c}	IC_{50}^{d} (μM)	
Trigocherrin A (2012) [31]	 **14**	35	1.5	23.3	–	Unknown
12-*O*-tetradecanoyl-phorbol-13-acetate (2012) [32]	 **15**	5.7	0.0029	1965	–	Possible activation of the signal transduction enzyme protein kinase C
Class E. Flavagline						
FL23(2015) [33]	 **16**	90.2 (nM)	–	–	~5 (nM)	Interference with the binding of prohibitin-1

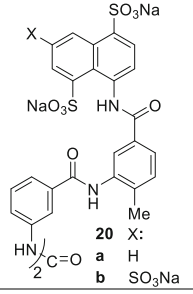
(continued)

Table 1 (continued)

Name (trade name) (year reported)	Structure	Antiviral activities				Mechanism of action
		CC_{50}^{a} (μM)	EC_{50}^{b} (μM)	SI^{c}	IC_{50}^{d} (μM)	
FL3 (2015) [33]	 **17**	119 (nM)	–	–	22.4 (nM)	Interference with the binding of prohibitin-1
Others						
CND0335 (2013) [34]	 **18**	>50	3.3	>15	–	Unknown
(α-carbonyl)hydrazone (2013) [35]	 **19**	101	3.2	32	–	Unknown

(continued)

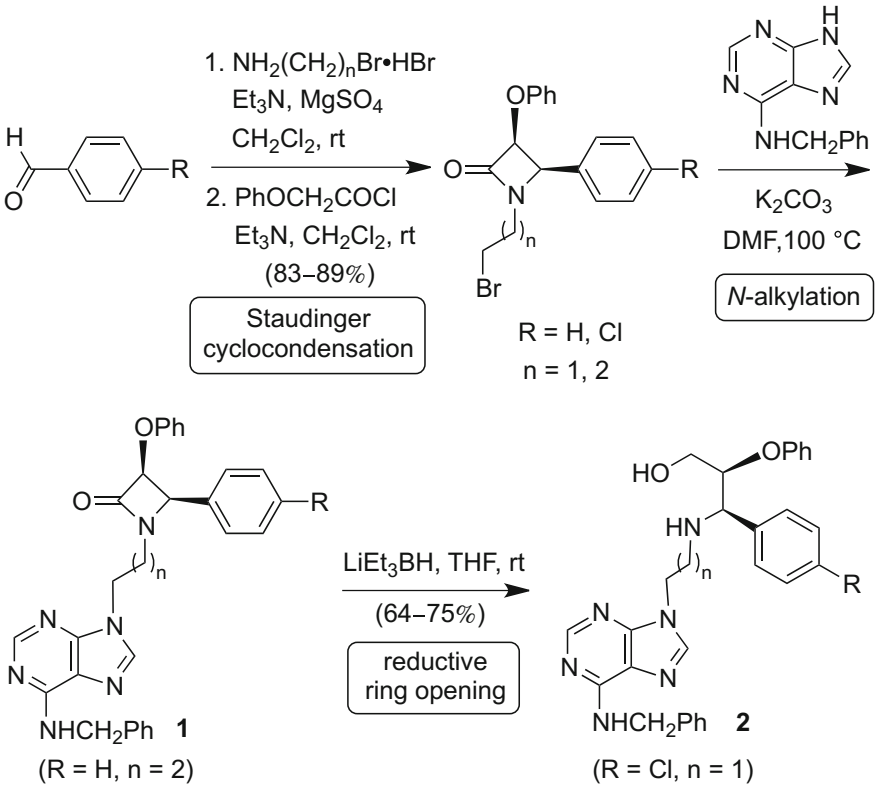
Table 1 (continued)

Name (trade name) (year reported)	Structure	Antiviral activities				Mechanism of action
		CC_{50}^{a} (μM)	EC_{50}^{b} (μM)	SI[c]	IC_{50}^{d} (μM)	
Suramin (Antrypol, 309 F, 309 Fourneau, Bayer 205, Moranyl, Naganin, Naganine) (2015) [36]		**a**				Inhibition of RNA synthesis, post-attachment step of viral entry, and (re)initiation of RNA synthesis
		>800	210	>3.8	–	
		b				
		>800	79	>10.1	~5	

[a]The concentration of a compound with an adverse effect of 50% was observed on the host cell metabolism, as determined by the MTS method
[b]The concentration of a compound at which virus replication was inhibited by 50% was observed, as determined by real-time quantitative RT–PCR
[c]Selectivity index
[d]Related information are available in original papers

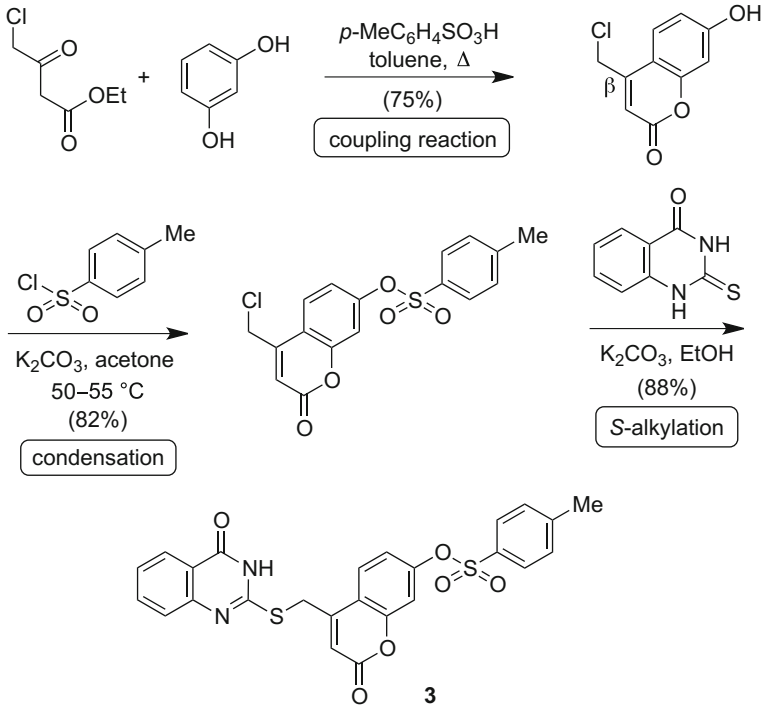
including CHIKV. In 2012, they reported purine β–lactam **1** and purine–amino-propanol **2** with symptom against CHIKV. The key steps for their synthesis shown in Scheme 1 include a Staudinger [2 + 2] cyclocondensation between a Schiff base and a ketene (from $PhOCH_2COCl$) to give a (ω-bromoalkyl)-*cis*-β-lactam with diastereoselectivity. Then *N*-alkylation of a purine derivative with this β-lactam intermediate gives the desired purine–β-lactam **1**. Furthermore, a $LiEt_3BH$-mediated β-lactam ring opening takes place to produce the target purine **2**.

In 2015, Hwu, Tsay, Neyts, and co-workers [22] reported the design and synthesis of a new series of uracil–coumarin–arene conjugates against CHIKV. Five of 22 new hybrid conjugates can inhibit CHIKV in Vero cells with significant potency and low toxicity. As shown in Scheme 2, their synthesis includes a coupling reaction to form a coumarin derivative, its condensation with an organosulfonyl chloride to give sulfonylated intermediate, and a selective *S*-alkylation of 2-thiobenzouracil at the allylic position of (coumarinyl)chloride to yield the desired triply conjugated target **3**. Its molecular framework is determined unambiguously by single X-ray diffraction analysis.



Scheme 1 Synthesis of purine–β-lactam **1** and purine–aminopropanol **2**

The coumarin moiety, $–SCH_2–$, and $–SO_2–$ (but not $–CH_2–$) joints in the conjugated compounds shown in Fig. 1 are essential to their antiviral activity. Use of either an Me or an NO_2 group attached to the arene moiety brings enhanced activity



Scheme 2 Synthesis of benzouracil–coumarin–arene conjugates **3**

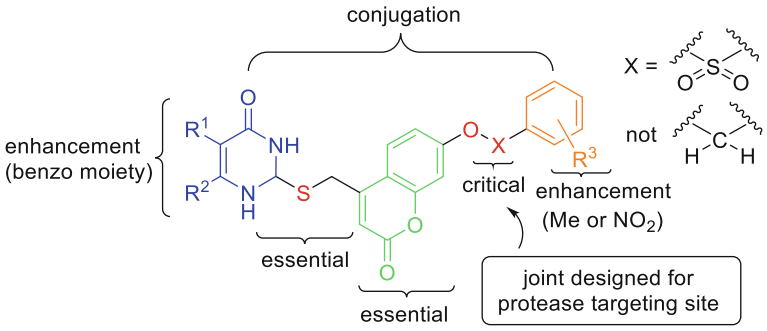


Fig. 1 Structure-activity relationship of uracil–coumarin–arene conjugates

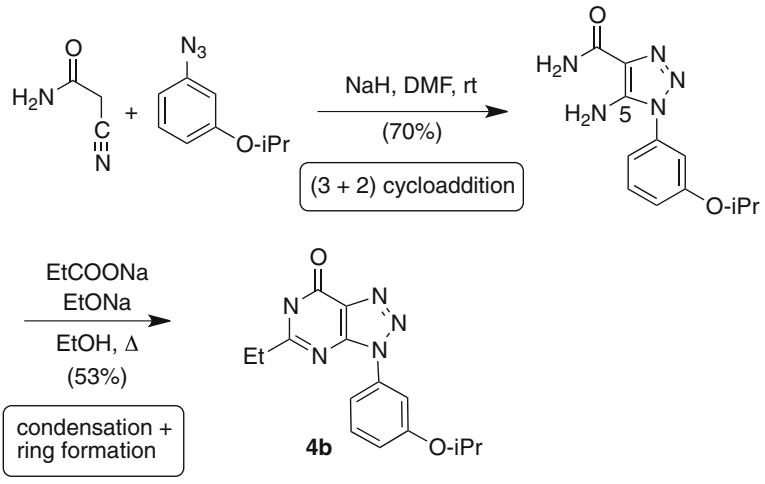
to the target molecules. When coumarin–arenes are conjugated with benzouracil, the resultant hybrids (such as **3**) exhibit better selectivity indexes than their kin with uracil or 5-methyluracil.

In 2014, Pérez–Pérez et al. [23] identified [1,2,3]triazolo[4,5-*d*]pyrimidin-7(6*H*)-ones as active inhibitors of CHIKV replication in the low micromolar range with no cytotoxicity detected up to 668 μM. The synthetic procedure for the most active compounds **4b** as shown in Scheme 3 includes (3 + 2) cycloaddition between an arylazide and a cyanoacetamide to give a 5-aminotriazole amide. Subsequent condensation followed by ring formation produces the target triazolopyrimidine **4b**.

B. Nucleosides

During the past five decades, nucleosides have been used in clinics and, nowadays, become cornerstones of treatment for patients with viral infections. Two drugs in this family were reported with anti-CHIKV activity in 2004 [24]. Ribavirin (**5**), a "synthetic nucleoside" containing a 1*H*-1,2,4-triazole moiety, is effective against a variety of RNA viruses, especially in the genus *Alphavirus*. The combination of ribavirin and interferon-α shows a synergistic anti-chikungunya viral effect [24]. Several studies have elucidated the mechanisms of anti-viral action of ribavirin. They involve predominantly inhibition of inosine monophosphate dehydrogenase (IMPDH) activity, depletion of the intracellular guanosine triphosphate (GTP) pools, inhibition of viral RNA capping, and induction of an error catastrophe [14, 37–39].

6-Azauridine (**6**) [24], containing a 1,2,4-triazine-3,5(2*H*,4*H*)-dione moiety, is an another "synthetic nucleoside" with a broad-spectrum of anti-metabolite. It inhibits both DNA and RNA virus replication. In comparison with ribavirin (**5**), 6-azauridine (**6**) shows a greater potency against CHIKV with EC_{50} = 0.82 μM and



Scheme 3 Synthesis of triazolopyrimidine **4b**

SI = 254. Its activity might be through the inhibition of orotidine monophosphate decarboxylase activity and the depletion of uridine triphosphate pools [40].

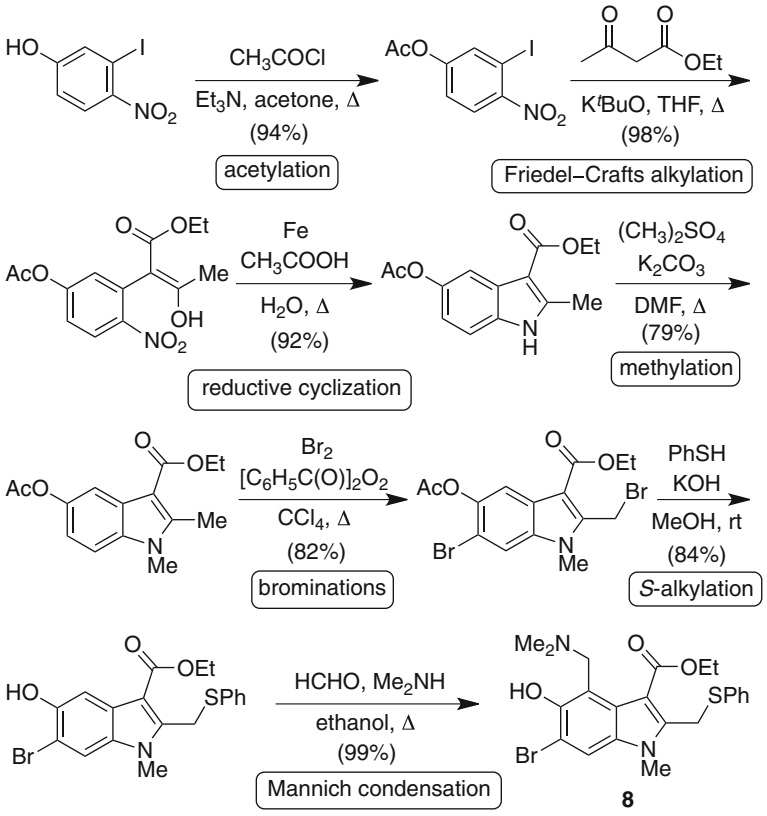
C. Alkaloids

Favipiravir (**7**) is a pyrazinecarboxamide derivative, which was discovered and synthesized by Toyama Chemical Co. in Japan as a candidate antiviral drug [41]. It is active against many viruses, including influenza viruses, West Nile virus, yellow fever virus, foot-and-mouth disease virus, flaviviruses, arenaviruses, bunyaviruses, alphaviruses, picornavirus and norovirus [41, 42]. In 2014, favipiravir (**7**) was approved in Japan for the treatment of influenza virus disease. The mechanism of its action is related to the selective inhibition of viral RNA-dependent RNA polymerase. In the same year, Neyts et al. [25] disclosed that favipiravir (**7**) inhibits viral genome replication of laboratory strains and clinical isolates of CHIKV.

The antiviral drug umifenovir (i.e., arbidol, **8**), an indole derivative, was originally developed at the Research Institute of Pharmaceutical Chemistry in Russia about three decades ago [43]. Since 1990, this drug has been used in Russia mainly for the intervention of prophylaxis and acute respiratory infections like influenza [44, 45]. In 2011, Pastorino et al. [26] reported that umifenovir (**8**) presents potent inhibitory activity against CHIKV. The significant anti-viral activity of this drug may be attributed to the diverse mechanisms of action, including interference with the early stages of CHIKV attachment or entry or the replication cycle, as well as alterations of cellular membranes [44, 46]. A synthetic procedure leading to umifenovir (**8**) as illustrated in Scheme 4 includes seven steps, for which the key steps are the Friedel–Crafts alkylation, reductive cyclization, and the Mannich condenation [43, 47]. On the other hand, this drug can also be produced through four steps as shown in the synthetic route in Scheme 5. They involve Nenitzescu indole synthesis, acylation/bromination, *S*-alkylation, and the Mannich condensation [48, 49].

Recently, de Lamballerie, Jayaprakash et al. [27] reported a series of aryl alkylidene alkaloids, among which 1,3-thiazolidin-4-ones **9** and **10** showed anti-chikungunya activity with IC_{50} values of 0.42 and 6.8 μM. These two compounds can be synthesized by simple steps shown in Scheme 6 [50, 51]. The key step is the Knoevenagel condensation. Moreover, the authors performed molecular docking simulation of the active compound **9** with the X-ray crystal structure of CHIKV nsP2 protease. As a result, the mechanism of action may come from the protease inhibition.

Harringtonine (**11**) is a natural alkaloid isolated from the Japanese plum yew, *Cephalotaxus harringtonia* in only 0.0064% yield [52]. In 2013, Chu et al. [28]. reported that it exhibits potent anti-CHIKV activity with an EC_{50} value of 0.24 μM with minimal cytotoxicity. Harringtonine inhibits an early stage of the CHIKV replication cycle, affects CHIKV RNA production, and interferes with viral protein expression.



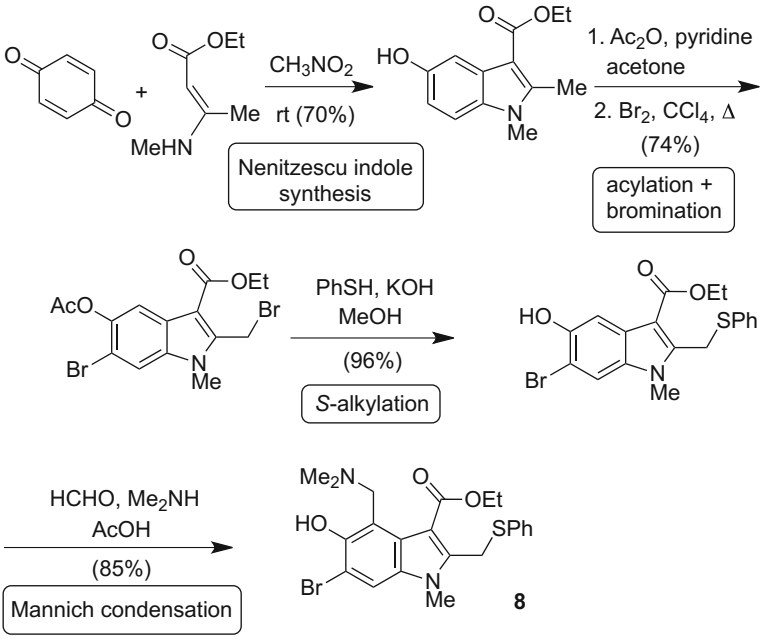
Scheme 4 Total synthesis of umifenovir (**8**)

D. Terpenoids

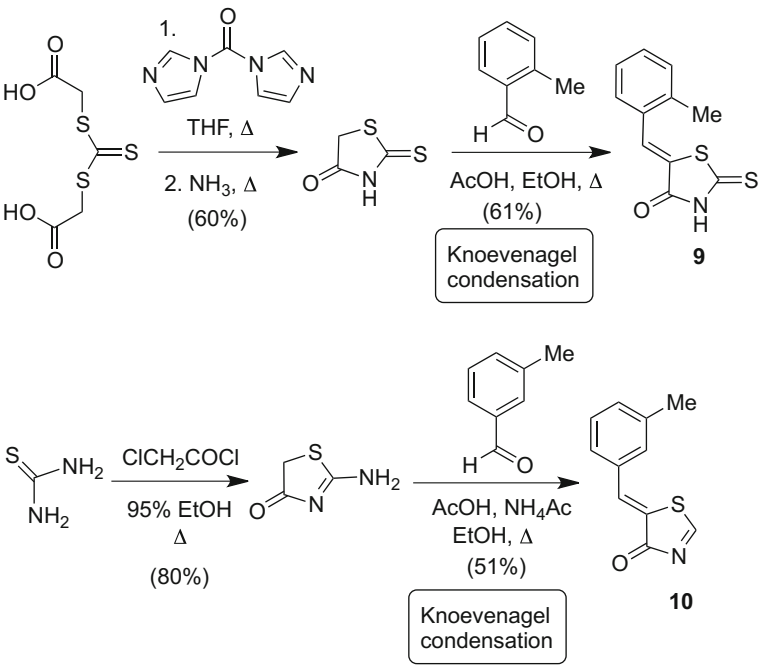
As a major class of natural compounds, terpenoids display a wide range of biological activity against a variety of infectious diseases. The four representatives shown in Table 1 contribute significantly to the anti-CHIKV development.

In 2014, Litaudon et al. [29] reported their isolation of diterpene jatrophane ester (**12**) in 0.0006% yield from the whole plant of *Euphorbia amygdaloides ssp. Semiperfoliata*, an endemic plant of Corsica and Sardinia. Jatrophane ester (**12**) shows an EC_{50} value of 0.76 μM with a high SI value of 208.

In the same year, Chu et al. [30] disclosed their isolation of two aplysiatoxin-related compounds **13a**,**b** from the marine cyanobacterium *Trichodesmium erythraeum* in ~0.0022% yield. These two 12-membered ring terpenes exhibit significant anti-CHIKV activity in post-treatment of infected SJCRH30 cells with EC_{50} values of 1.3 and 2.7 μM, respectively. Their potency is on the same order as that of the highly-oxygenated natural trigocherrin A (**14**) [31]. This chlorinated daphnane diterpene orthoester was isolated from the bark of *Trigonostemon cherrieri* in

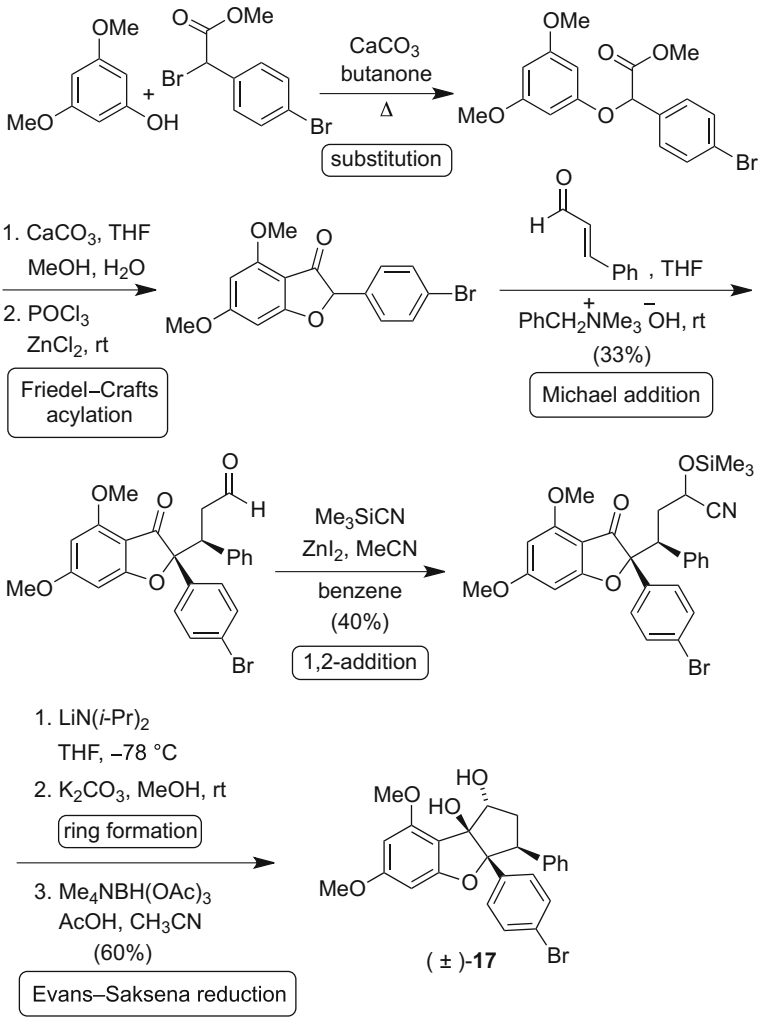


Scheme 5 Total synthesis of umifenovir (**8**)

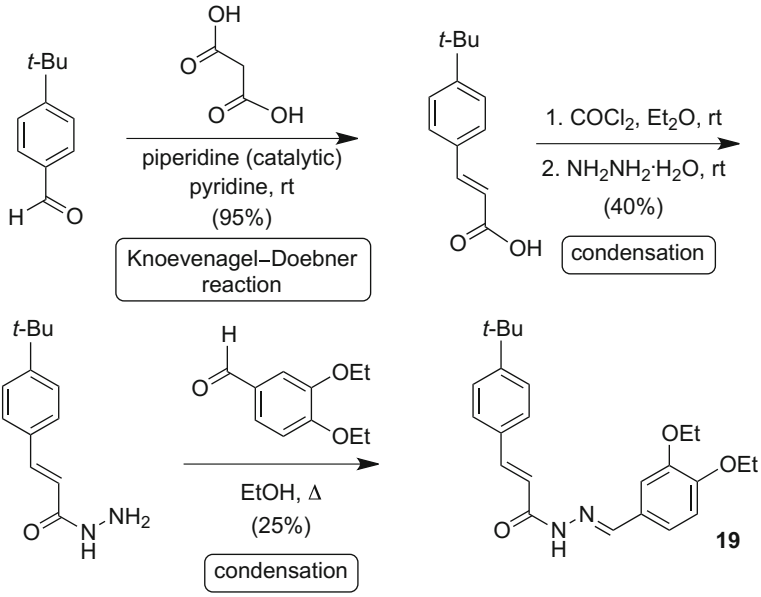


Scheme 6 Synthesis of 1,3-thiazolidin-4-ones **9** and **10**

0.00017% yield, an endemic plant of New Caledonia [53]. Nevertheless, they are much less potent in comparison with 12-*O*-tetradecanoylphorbol 13-acetate (**15**) [54], which was reported by Litaudon et al. in 2012 [32]. Tetradecanoyl phorbol acetate **15** presents an EC_{50} value of 2.9 nM with a very high SI value of 1965. The activation of the signal transduction enzyme protein kinase C could be the mechanism of action on its anti-CHIKV activity.



Scheme 7 Synthesis of flavagline (±)−**17**



Scheme 8 Preparation of (α-carbonyl)hydrazone **19**

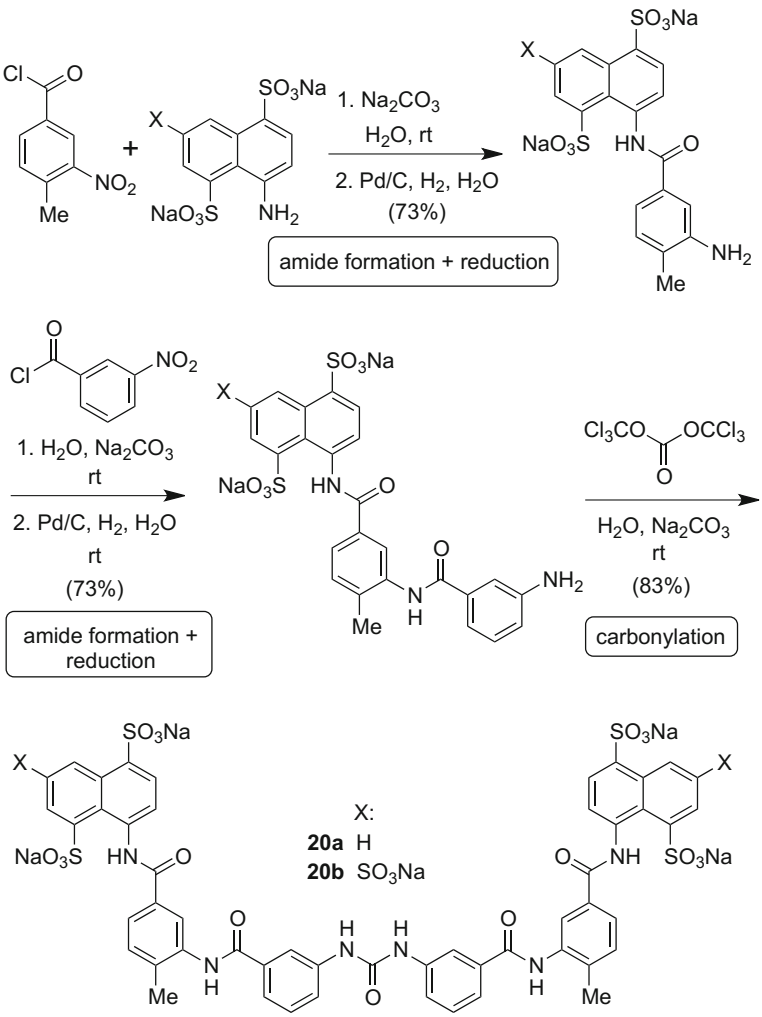
E. Flavagline

Plant natural products flavaglines are characterized with a unique cyclopenta [*b*]benzofuran nuclues. Fused benzofurans display an array of biological effects as insecticidal, antifungal, anti-inflammatory, and neuroprotective agents [55]. In 2015, Smith et al. [33] reported that flavaglines FL23 (**16**) and FL3 (**17**) inhibit the CHIKV by interaction with prohibitin-1, which is a receptor protein used by the virus to enter mammalian cells. The synthetic route to give flavaglines FL3 (±)-(**17**) is shown in Scheme 7. The key steps include the Friedel–Craft acylative cyclization, the Michael addition, and Evans–Saksena reduction reactions [56, 57].

Others

Apart from the above classes of compounds, Freitas–Junior et al. [34] screened a kinase inhibitor library of 4000 compounds against CHIKV infection by using high throughput screening. In 2013, they reported that four benzofuran derivatives were active as inhibitors associated with CHIKV cell death in a dose-dependent manner. Compounds with a scaffold as benzofuran **18** (CND0335) exhibit the EC_{50} values of between 2.2 and 7.1 μM.

Brancale et al. [35] reported their computer-aided identification and design of a series of (α-carbony)hydrazones with selective activity against CHIKV. They initially obtained the hit candidates from a virtual screening simulation of ∼5 million compounds on the CHIKV nsP2. After investigation of their structure–activity relationship in silico and optimization of the candidate compounds, a simplified



Scheme 9 Synthesis of suramin and its derivative **20a**,**b**

chemical structure (α-carbonyl)hydrazone **19** was attained. Synthesis of compound **19** is illustrated in Scheme 8, in which sequential Knoevenagel–Doebner reaction and condensation reactions are in operation. This compound indeed exhibits promising activity profile as shown in Table 1.

In 2015, van Hemert et al. [36] first reported that the approved anti-parasitic drug suramin (**20b**) inhibits CHIKV RNA synthesis with an IC_{50} value of ~5 μM. It also inhibits replication of various CHIKV isolates in cell culture with an EC_{50} of 79 μM and CC_{50} >800 μM. Furthermore, suramin can inhibit a post-attachment early step of the CHIKV replicative cycle and (re)initiation of CHIKV RNA synthesis by possibly interfering with binding of the template RNA. These findings are

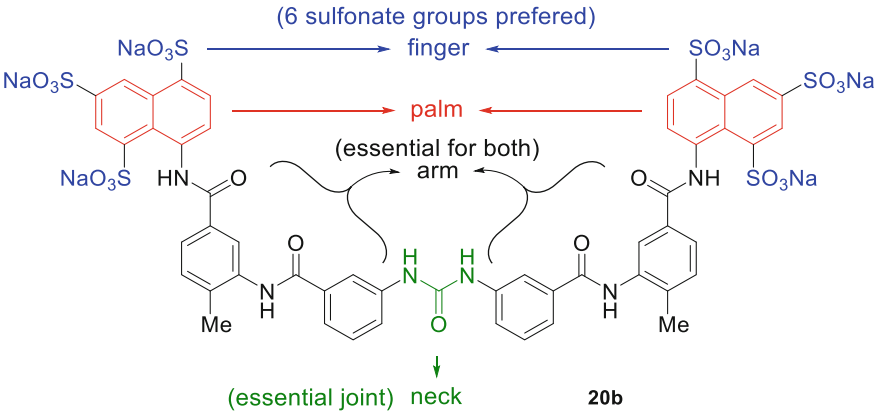


Fig. 2 Structure–activity relationship of suramin and its derivatives

in agreement with the previous studies in vitro that suramin inhibits RNA viral polymerases and helicases [36]. Very soon, closely related results on inhibition of the same virus entry and transmission by suramin (**20b**) is reported by Kuo, Lin et al. [58].

A series of suramin derivatives (e.g., **20a**) were synthesized by Bolognesi, Hwu et al. [59] based on the design of compounds with fewer sulfonate fingers, shorter arms, only one side, or no neck in comparison with suramin. As depicted in Scheme 9, the representative procedure includes amide formation, followed by reduction of nitro compounds and carbonylation. These suramin derivatives were also tested for their ability to inhibit CHIKV RNA synthesis in vitro. Unsymmetrical compounds possessing only one arm were inactive regardless of its length. It has been proved that compound with six sulfonate groups showed greater anti-CHIKV (EC_{50} = 79 μM) than tetrasulfonate (EC_{50} = 210 μM) in the cell culture (see Table 1 and Fig. 2).

3 Concluding Remarks

Development of new antiviral compounds for chikungunya fever meets an urgent need of global societies. It is due to the re-emerged outbreaks occurring in 2004 and recent spreading to the Americas in late 2013. A limited number of natural products exhibit great potency with an appealing selective index value. Unfortunately, their isolation yields are often very low, as represented by the naturally occurring 12-*O*-tetradecanoylphorbol 13-acetate (**15**) obtained in 0.00017% yield. Complex structures associated with these natural products with multiple stereogenic centers, various functional groups, and several rings make their total synthesis very challenging.

As a result, medicinal chemists, biologists, and virologists with interdisciplinary expertise have been seeking for unnatural targets that can be obtained in a large quantity by chemical synthesis. By far, various types of compounds with anti-CHIKV activity have been obtained; among which the ones reported recently are listed in the Table 1. These compounds belong to purine/pyrimidine, nucleoside, alkaloid, flavagline, etc. Nevertheless, none of them has been yet approved as a drug to serve the purpose. The opportunity remains high for scientists to devote their efforts to design and synthesize small molecules to fight for the human battle against CHIKV with success.

Moreover, some molecules in the compound libraries of the Table 1, such as benzouracil–coumarin–arene conjugates, suramin derivatives et al. may be suitable for their development to become potential new drugs for the treatment of neurodegenerative disorders. Multi-functional design, in silico computational screening, in vitro/ex vivo/in vivo experiments, and organic syntheses of these novel candidate compounds are in progress.

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