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Microwave-assisted, rapid synthesis of 2-vinylquinolines and evaluation of their antimalarial activity

Guang Huang^{a,1}, Claribel Murillo Solano^{b,1}, Yuxin Su^{c,d,1}, Nameer Ezzat^a, Shino Matsui^a, Liuyu Huang^d, Debopam Chakrabarti^{b,*}, Yu Yuan^{a,*}

^aDepartment of Chemistry, University of Central Florida, Orlando, FL, USA

^bDivision of Molecular Microbiology, Burnett School of Biomedical Sciences, University of Central Florida, Orlando, FL, USA

^cAcademy of Military Medical Science, Beijing, China

^dChinese PLA Center for Disease Control and Prevention, Beijing, China

Abstract

A rapid and efficient synthesis of 2-vinylquinolines via trifluoromethanesulfonamidemediated olefination of 2-methylquinoline and aldehyde under microwave irradiation is reported. Biological evaluation of these scaffolds demonstrates that 2-vinylquinolines **3x** – **3z** possess excellent antimalarial activities against chloroquine-resistant Dd2 strain of *Plasmodium falciparum* (IC₅₀ < 100 nM).

Graphical Abstract

Keywords

2-vinylquinoline; 2-methylquinoline; olefination; microwave-assisted synthesis; antimalarial

*Corresponding author. Debopam.Chakrabarti@ucf.edu (D. Chakrabarti); Yu.Yuan@ucf.edu (Y. Yuan).

¹These authors contribute equally to this work.

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Supplementary data

Supplementary data associated with this article can be found.

Introduction

Quinoline as a unique heterocyclic scaffold has found broad applications in medicinal chemistry, as well as material science and agrochemical industries [1]. For example, aminoquinolines such as chloroquine (CQ), amodiaquine (AQ) and piperazine (PQ) are clinical antimalarial drugs; hydroxyquinolines are excellent metal chelators as well as important precursors for agrochemical production; and *N*-alkylated quinoline dyes are versatile tools for biological studies. Among quinoline derivatives, 2-vinylquinolines exhibit a wide range of pharmacological activities, as exemplified by antileishmanial agent chimanine (**A1**) [2], anticancer compound **A2** [3], integrase inhibitor FZ41 (**A3**) [4], CysLT1 antagonist VUF 5017 (**A4**) [5] and antimalarial agent UCF 501 (**A5**) [6] (Fig. 1).

Owing to their biological significance, the synthesis of 2-vinylquinolines has attracted great attention from the chemistry community. The double bond is most conveniently prepared from a Wittig reaction between 2-quinolinecarboxaldehydes and the corresponding ylides (Scheme 1a) [7]. Nevertheless, the limited availability of 2-quinolinecarboxaldehyde narrows the scope of this approach, and the stoichiometric amount of phosphine oxide byproduct further complicates the purification. Alternatively, treatment of quinoline *N*-oxide with styrenes by reductive olefination or with boronic acids via cross-coupling reaction can selectively afford *trans*-2-vinylquinolines (Scheme 1b) [8]. The downside of such transformations lies in the high cost of the metal catalyst and the unsatisfactory yields. In addition, these olefination reactions also require long reaction times and excessive amounts of the starting material.

From reagent cost and substrate availability perspectives, the most effective methodology for the preparation of 2-vinylquinolines is the direct condensation of 2-methylquinolines with proper aldehydes (Scheme 1c) [9]. However, this formal aldoltype condensation requires long reaction time, high temperature or a metal catalyst, furnishing 2-vinylquinolines in only modest isolated yields. To address this challenge, many research groups have explored alternative imine surrogates and Mannich type reactions (Scheme 1d). Wang and coworkers [10] reported *N*-bromosuccinimide (NBS)/ *tert*-butyl hydroperoxide (TBHP) mediated construction of 2-alkenylquinoline through an oxidative condensation-deamination process. Tian group [11] disclosed a related olefination of secondary amines and 2-methylquinoline in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Recently, Huang et al [12] developed an ironcatalyzed synthesis of *trans*-2-vinylquinolines initiated by nucleophilic addition of 2-methylquinolines to *N*-sulfonylaldimines. In addition, Wang [13] accomplished *trans*-alkenylazaarene synthesis by reacting with *in situ* generated *N*-sulfonylaldimines. These transformations greatly enriched the synthetic chemist's toolbox, but *rapid* reactions requiring no pre-formation of imines and organometallic catalysts are still highly desirable.

During the course of our investigation of 2-styrylquinolines as potential antimalarial agents [6], we aimed to establish the preliminary structure–activity relationships (SARs) at the C2 position by screening different arylvinyl groups. Herein, we report a rapid synthesis of 2-vinylquinolines via trifluoromethanesulfonamide (TfNH₂)-mediated olefination under

microwave irradiation (Scheme 1e) and the *in vitro* evaluation of these compounds against Dd2 strain of *Plasmodium falciparum*.

Initially, the optimization was carried out using 2-methylquinoline **1a** and benzaldehyde **2a** under microwave irradiation (Table 1). The additives played a crucial role in the olefination reaction. For instance, the desired product was obtained in low yields (13–30%) in the absence of any additive even with excess of aldehyde (Table 1, entries 1–5); in contrast, the addition of sulfonamides significantly boosted the yield of **3a** (entries 6–11). Among the screened additives, TfNH₂ was proved to be the most effective (entries 8 and 11). Further investigation of solvents and additive stoichiometry revealed that dimethylformamide (DMF) was the optimal solvent and 1.2 equivalents of TfNH₂ provided the best yield of the 2-vinylquinoline (entry 12). The optimization of other reaction parameters such as temperature and irradiation time quickly established that the olefination reaction was best conducted at 140 °C for 20 min (entry 16). No further improvement was observed when higher temperature or shorter reaction time were adopted (entries 14 and 17–20).

With the optimized conditions in hand, we investigated the generality of this methodology (Table 2). The reaction of 6-methoxy-2-methylquinoline with different aromatic aldehydes smoothly provided the desired products **3b**–**3e** in excellent yields. Aliphatic aldehydes (butyraldehyde and isovaleraldehyde) were valid substrates as well, although the corresponding products **3f** and **3g** were isolated in moderate yields. We also found that substitutions at the C4 position of the methylquinoline, including chloride, aniline and aliphatic amines, were compatible with current microwave assisted conditions. In general, chloro and phenylamino groups at the C4 position decreased the reaction yields and alkyl amines retained the high yields of 2-vinylquinolines. The scope of aldehydes was not limited to simple benzaldehydes and aliphatic aldehydes, heteroaromatics aldehydes such as pyridinecarboxaldehyde and thiophenecarboxaldehyde were also good substrates for the olefination. In line with the previous study [13], a plausible mechanism for olefination is outlined in Scheme 2. Under our microwave conditions, TfNH₂ is optimal for *in situ* aldime formation and facilitates the subsequent elimination.

The newly synthesized compounds **3a**–**3z** were evaluated for their *in vitro* antimalarial activity against chloroquine-resistant *Plasmodium falciparum* Dd2 strain by SYBR green I-based DNA quantification assay, using chloroquine as a positive control. As shown in Table 3, compounds **3a**–**3h** exhibited low activity against Dd2 strain (IC₅₀ > 10 μM). Attachment of phenylamino or cyclohexylamino groups at the C4 position improved antimalarial activity to the low micromolar range. For instance, compound **3i** (IC₅₀ = 0.168 ± 0.001 μM) and **3m** (IC₅₀ = 0.227 ± 0.020 μM) showed comparable activity to chloroquine (IC₅₀ = 0.172 μM). Other simple amino groups incorporated into the C4 position, such as morpholinyl and piperidyl groups abolished antiplasmodial activity, as demonstrated by compounds **3n**–**3p** (IC₅₀ > 10 μM), whereas analogues with pyrrolyl, 1-methylpiperidyl, *N*-(2-hydroxyethyl) piperidyl and dimethylamino groups at C4 position exhibited good activity against Dd2 strains with IC₅₀ values ranging from 0.367 ± 0.052 to 0.672 ± 0.011 μM, except for compound **3w**. In particular, compounds **3x**–**3z** were found to be more potent than chloroquine toward Dd2 strain (IC₅₀ < 0.1 μM). It is worth noting that **1l**, an aminoquinoline without a vinyl group (IC₅₀ = 5.516 ± 0.571 μM) is significantly less potent than **3x**, **3y** and

3z, indicating that alkene motifs at the C2 position are vital to the antimalarial potency of aminoquinolines.

Conclusions

In summary, we have explored the chemical space at quinoline's C2 position with various vinyl substituents. Access to such scaffolds is achieved by a rapid olefination reaction mediated by TiNH_2 under microwave irradiation. Compared to previous approaches, our current method demonstrates broad substrate scope, mild conditions and superior reaction kinetics. With this method, we have prepared a diverse range of vinylquinoline analogues, some of which exhibit excellent antimalarial activity. Further medicinal chemistry optimizations are currently underway to identify potent candidates for the treatment of malaria infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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- Direct olefination of 2-methylquinoline under microwave irradiation
- Broad substrate scope, excellent reaction kinetics
- Potent antimalarial activity against chloroquine-resistant strain

Fig. 1.
Representative examples of bioactive 2-vinylquinolines.

Previous work:

This work:

Scheme 1.

Synthesis of 2-vinylquinolines During the course of our investigation of 2-styrylquinolines as potential antimalarial

Scheme 2.
Plausible mechanism for formation of 2-vinylquinoline **3**

Table 1

Optimization of reaction conditions

entry	solvent	additive	equiv. ^a	t (°C)	time (min)	yield (%) ^b
1	DMF	-	3	130	30	19
2	DMF	-	5	130	30	30
3	1,4-dioxane	-	5	130	30	13
4	xylene	-	5	130	30	26
5	DMSO	-	5	130	30	22
6	xylene	carzenide	3	130	30	45
7	xylene	<i>p</i> -TsNH ₂	3	130	30	72
8	xylene	TfNH ₂	3	130	30	81
9	DMF	carzenide	3	130	30	64
10	DMF	<i>p</i> -TsNH ₂	3	130	30	82
11	DMF	TfNH ₂	3	130	30	89
12	DMF	TfNH ₂	1.2	130	30	92
13	DMF	TfNH ₂	1	130	30	83
14	DMF	TfNH ₂	1.2	130	20	73
15	DMF	TfNH ₂	1.2	140	30	86
16	DMF	TfNH ₂	1.2	140	20	93
17	DMF	TfNH ₂	1.2	140	10	82
18	DMF	TfNH ₂	1.2	150	20	84
19	DMF	TfNH ₂	1.2	160	20	75
20	DMF	TfNH ₂	1.2	160	10	83

^aRepresents the amount of benzaldehyde **2a**^bIsolated yield

Table 2

Substrate scope of olefination under microwave irradiation.

<p>3a: 93% yield</p>	<p>3b: R = phenyl, 95% yield 3c: R = 4-dimethylaminophenyl, 94% yield 3d: R = 4-nitrophenyl, 91% yield 3e: R = 4-pyridyl, 87% yield 3f: R = propyl, 54% yield 3g: R = isobutyl, 60% yield</p>	<p>3h: R = 4-nitrophenyl, 51% yield 3i: R = 4-pyridyl, 43% yield</p>
<p>3j: R = 4-nitrophenyl, 55% yield 3k: R = 4-pyridyl, 48% yield</p>	<p>3l: R = 4-nitrophenyl, 91% yield 3m: R = 4-pyridyl, 85% yield</p>	<p>3n: R = 4-nitrophenyl, 93% yield 3o: R = 4-pyridyl, 87% yield</p>
<p>3p: R = 4-nitrophenyl, 90% yield 3q: R = 4-pyridyl, 88% yield</p>	<p>3r: R = 4-nitrophenyl, 91% yield 3s: R = 4-pyridyl, 85% yield</p>	<p>3t: R = 4-nitrophenyl, 84% yield 3u: R = 4-pyridyl, 87% yield</p>
<p>3v: R = 4-nitrophenyl, 83% yield 3w: R = 4-pyridyl, 80% yield</p>	<p>3x: R = 4-pyridyl, 83% yield 3y: R = 2-thienyl, 88% yield 3z: R = 4-bromophenyl, 92% yield</p>	

Table 3*In vitro* antimalarial activity of **3a–3z** against Dd2 strain

Compd.	Dd2 IC ₅₀ (μM) ^a	Compd.	Dd2 IC ₅₀ (μM) ^a
3a	>10.0 ^b	3o	>10.0 ^b
3b	>10.0 ^b	3p	>10.0 ^b
3c	>10.0 ^b	3q	4.895 ± 1.043
3d	>10.0 ^b	3r	0.493 ± 0.092
3e	>10.0 ^b	3s	0.367 ± 0.052
3f	>10.0 ^b	3t	0.452 ± 0.087
3g	>10.0 ^b	3u	0.610 ± 0.069
3h	>10.0 ^b	3v	0.672 ± 0.011
3i	2.540 ± 0.434	3w	>10.0 ^b
3j	0.509 ± 0.052	3x	0.033 ± 0.007
3k	0.965 ± 0.167	3y	0.096 ± 0.005
3l	0.171 ± 0.001	3z	0.040 ± 0.010
3m	0.277 ± 0.020	11 ^c	5.516 ± 0.571
3n	>10.0 ^b	Chloroquine	0.172

^aValues are mean of n = 3.^b>IC₅₀ value is above the highest concentration used in the assay.^csee supplemental data for structure.