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

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Abstract

A rapid and efficient synthesis of 2-vinylquinolines via trifluoromethanesulfonamide-mediated 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* (IC_{50} < 100 nM).

Keywords

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

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 piperaquine (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).

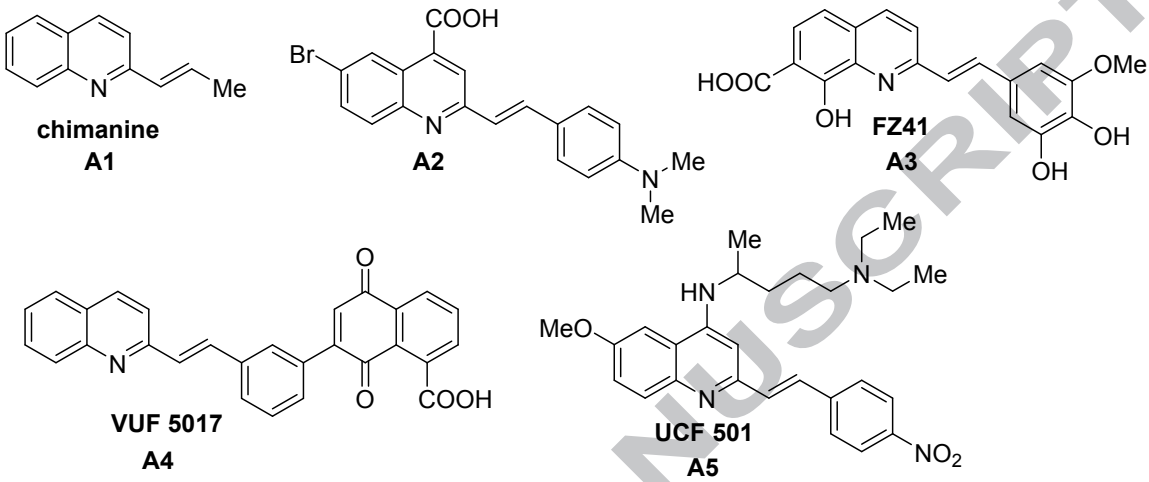
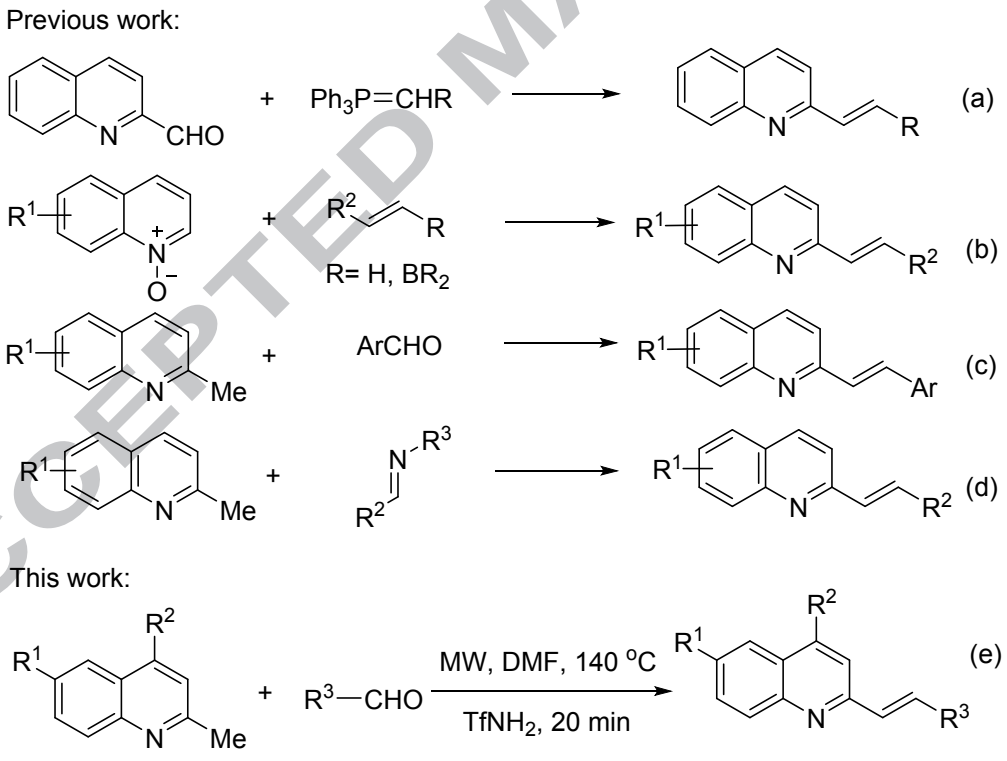


Fig. 1. Representative examples of bioactive 2-vinylquinolines.

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 aldol-type 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-alkenlyquinoline 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 iron-catalyzed 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.



Scheme 1. Synthesis of 2-vinylquinolines

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 ($TfNH_2$)-mediated olefination under microwave irradiation (Scheme 1e) and the *in vitro* evaluation of these compounds against Dd2 strain of *Plasmodium falciparum*.

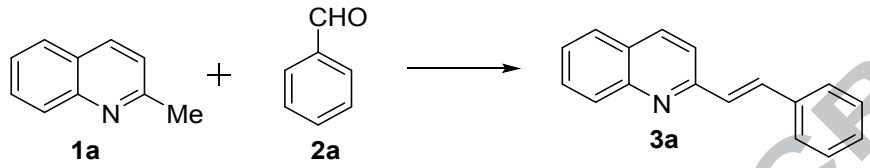
Initially, the optimization was carried out using 2-methylquinoline **1a** and benzaldehyde **2a** under microwave irradiation (Table 1). The additives played a crucial role in the olefination reaction. For instance, the desired product was obtained in low yields (13-30%) in the absence of any additive 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, $TfNH_2$ 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 $TfNH_2$ 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 ºC 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, $TfNH_2$ is optimal for *in situ* aldimine formation and facilitates the subsequent elimination.

Table 1

Optimization of reaction conditions



1a **2a** **3a**

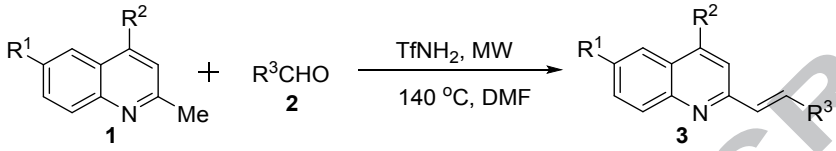
entry	solvent	additive	equiv. [a]	t (°C)	time (min)	yield (%) [b]
1	DMF	-	3	130	30	19
2	DMF	-	5	130	30	30
3	1,4-dioxane	-	5	130	30	13
4	xylene	-	5	130	30	26
5	DMSO	-	5	130	30	22
6	xylene	carzenide	3	130	30	45
7	xylene	*p*-$TsNH_2$	3	130	30	72
8	xylene	$TfNH_2$	3	130	30	81
9	DMF	carzenide	3	130	30	64
10	DMF	*p*-$TsNH_2$	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

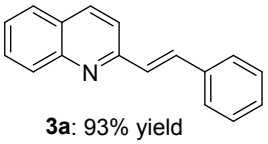
[a] Represents the amount of benzaldehyde **2a**

[b] Isolated yield

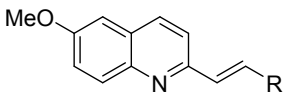
Table 2

Substrate scope of olefination under microwave irradiation.

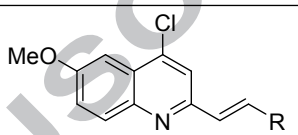




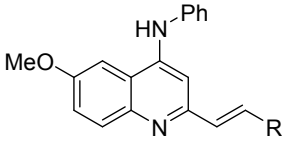
3a: 93% yield



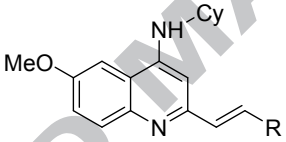
3b: R = phenyl, 95% yield
3c: R = 4-dimethylaminophenyl, 94% yield
3d: R = 4-nitrophenyl, 91% yield
3e: R = 4-pyridyl, 87% yield
3f: R = propyl, 54% yield
3g: R = isobutyl, 60% yield



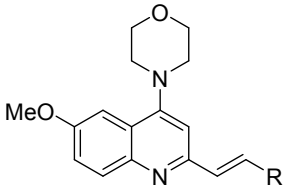
3h: R = 4-nitrophenyl, 51% yield
3i: R = 4-pyridyl, 43% yield



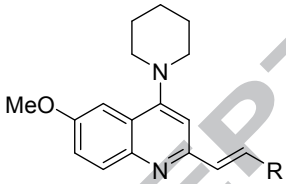
3j: R = 4-nitrophenyl, 55% yield
3k: R = 4-pyridyl, 48% yield



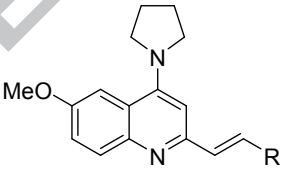
3l: R = 4-nitrophenyl, 91% yield
3m: R = 4-pyridyl, 85% yield



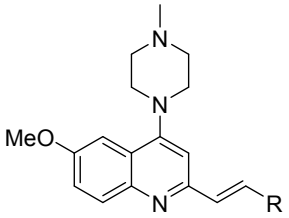
3n: R = 4-nitrophenyl, 93% yield
3o: R = 4-pyridyl, 87% yield



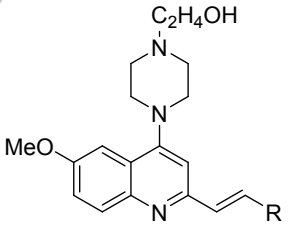
3p: R = 4-nitrophenyl, 90% yield
3q: R = 4-pyridyl, 88% yield



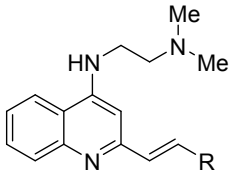
3r: R = 4-nitrophenyl, 91% yield
3s: R = 4-pyridyl, 85% yield



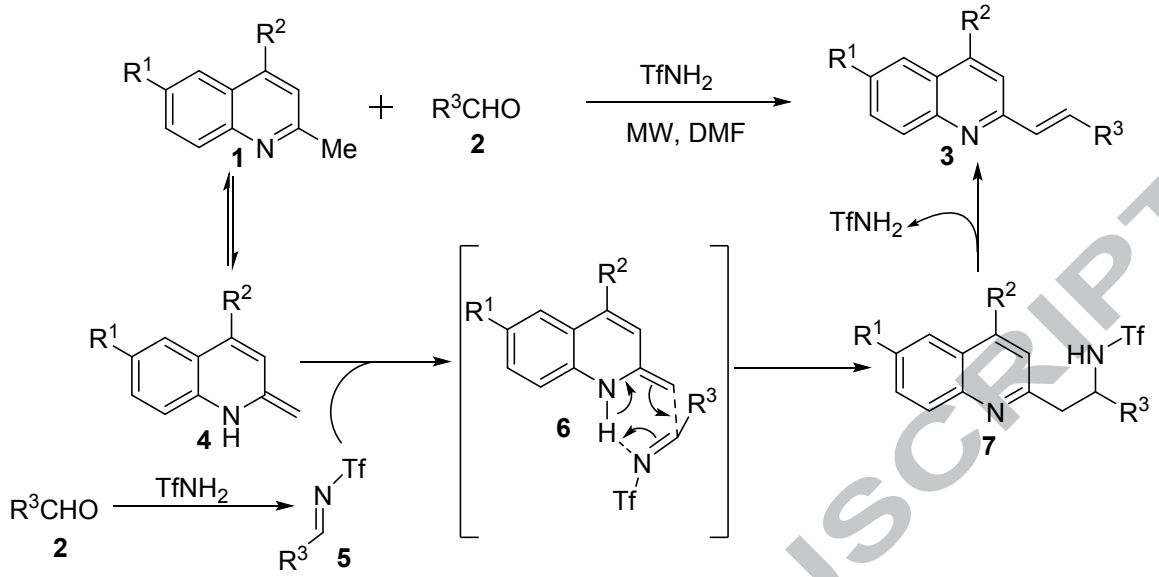
3t: R = 4-nitrophenyl, 84% yield
3u: R = 4-pyridyl, 87% yield



3v: R = 4-nitrophenyl, 83% yield
3w: R = 4-pyridyl, 80% yield



3x: R = 4-pyridyl, 83% yield
3y: R = 2-thienyl, 88% yield
3z: R = 4-bromophenyl, 92% yield



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

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 (IC_{50} > 10 μM). Attachment of phenylamino or cyclohexylamino groups at the C4 position improved antimalarial activity to the low micromolar range. For instance, compound **3l** (IC_{50} = 0.168 ± 0.001 μM) and **3m** (IC_{50} = 0.227 ± 0.020 μM) showed comparable activity to chloroquine (IC_{50} = 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** (IC_{50} > 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 IC_{50} 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 (IC_{50} < 0.1 μM). It is worth noting that 1**l**, an aminoquinoline without a vinyl group (IC_{50} = 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.

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	**1l** [c]	5.516 ± 0.571
3n	>10.0 [b]	**Chloroquine**	0.172

[a]Values are mean of n ≥ 3.

[b]>IC_{50} value is above the highest concentration used in the assay.

[c] see supplemental data for structure.

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 $TfNH_2$ 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.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found.

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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