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A new procedure for N^1-alkylation of imidazolidin-4-ones and its NMR characterization

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ABSTRACT

N^1-unsubstituted imidazolidin-4-ones of primaquine (PQ) can be stabilized by N^1-alkylation under basic conditions. Here we report the development, with our conditions, of peptidomimetic derivatives of PQ with L-amino acid and alkyl derivatives. The new derivatives represent potential new therapeutics for use against protozoan parasites, through enzymatic protection of aminopeptidases.

1. Introduction

In the last 30 years the pentagonal structure of imidazolidin-4-one has been employed with some regularity in medicinal chemistry. A possible approach to diminish problems with peptides including poor penetration of biomembranes, rapid enzymatic degradation and short biological half-life was to produce prodrugs or more lipophilic forms than the parent peptides. To this end, Bundgaard and co-workers reported the imidazolidin-4-one formation by condensing peptides with a free *N*-terminal amino group with aldehyde or ketones (Scheme 1). The derivatives exhibit bioreversibility by conversion to the parent peptide by spontaneous hydrolysis and almost complete resistance to enzymatic cleavage [1–4]. Equally relevant was the application of this strategy of condensation between the carbonyl compounds and the α-aminoamide side chain function of ampicillin [5].

Many reports on imidazolidin-4-ones deal with formation of tertiary amide and secondary amine in the pentagonal ring, as illustrated in Scheme 1. N^1-unsubstituted imidazolidin-4-ones can be stabilized by non-stereoselective formation of a salt or by acylation. The ring variation of substituent in −NH− group and formation of amide linker has been developed in our research group in that secondary amine of imidazolidin-4-one was condensed with L-amino acids [6–8]. With this strategy, we anticipate reduced exposure to aminopeptidases as the consequence of elimination of the amide bond in our peptidomimetic antimalarial derivatives and, for the first time, reveal imidazolidin-4-ones as a new alkylating agent. The literature includes just nine reports that focus on the reactivity of the secondary amine of imidazolidin-4-one for tertiary amine formation. Eight of these manuscripts reported intramolecular cyclization [9–16] and only one involved N^1-alkylation through aza-Michael addition [17]. Under acidic conditions, N^1-unsubstituted imidazolidin-4-ones were treated with methyl vinyl ketone as Michael acceptor to give a mixture of two diastereomers (14:1 and 12:1), that was due to the utilization of chiral amino amides [17]. For the first time, and using basic conditions, now we report N^1-alkylation of imidazolidin-4-ones using diverse alkylating agents.

2. Results and discussion

The starting imidazolidin-4-one (**1**, Scheme 2) was prepared from our previous work, in that primaquine (PQ) was condensed with Boc-Gly-OH to yield the corresponding N^{α}-Boc-protected glycylPQ. Acidolytic removal of Boc to yield glycylPQ by using trifluoroacetic acid (TFA) and this was then reacted with propanone in refluxing with methanol, by a previously described method [18], to yield compound **1** (Scheme 2). This imidazolidin-4-one **1** was then added to *N*-(bromoalkyl)phthalimide to produce derivative **2** (Scheme 2), bromo-*N*,*N*-diethylethylamine to **3** or bromo-alkanes

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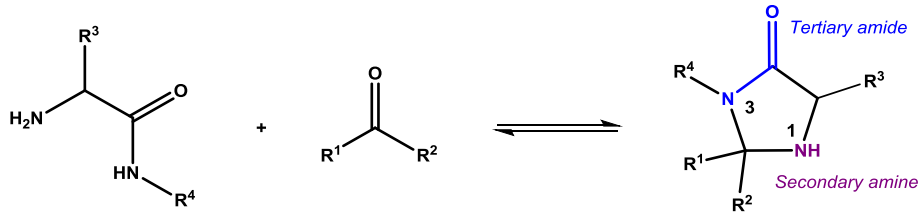
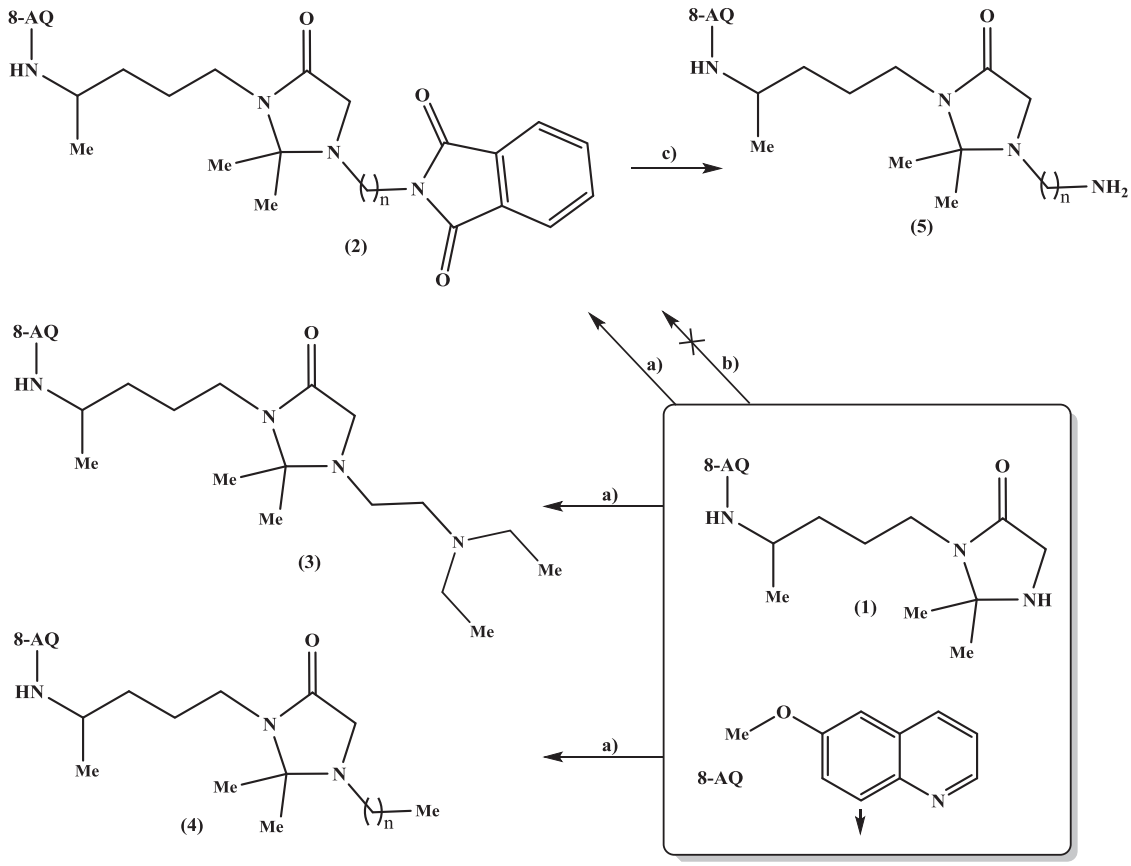


Scheme 1. Imidazolidin-4-one formation by condensing peptides with a free N-terminal amino group with aldehyde or ketones.



Scheme 2. General scheme for N^1-alkylation of imidazolidin-4-ones. Methods a), b) and c) are described in Experimental Section.

to **4**, and heated at 120 °C for 24 h. The presence of a non-nucleophilic tertiary amine (Et_3N) retains the basic pH and under solvent-free conditions. Also relevant to this method was a selective *N*-alkylation of imidazolidin-4-one and not in N^8-quinoline ring of PQ, an essential group to drug activity [19]. The variation of alkyl agent was used to produce similar compounds to imidazoquines, according to molecular mass and imidazolidin-4-one core [19].

The yields for the formation of derivatives **2**–**4** are listed in Table 1. Considering cyclic amine (secondary) in **1** and associated with some steric effects of alkyl chains we can understand differences to yields for derivatives with phthalimide group. To improve this yield, a method was applied involving Cs_2CO_3 in that cesium base did not promote alkylation of primary amines but rather suppressed over alkylations of the secondary amine product [20]. However, it was not possible to obtain the intended **2c** compound, and this result was also obtained with the use of one equivalent of alkylating agent in the presence of a solvent such as acetonitrile. Accordingly we conclude that harsh conditions such as elevated temperature and stronger catalysts were needed.

During optimization of method a, increasing the quantity of bromo-derivative added and extending the duration of the reaction resulted in formation of two new compounds at *m*/*z* 413 and *m*/*z* 719. To the first (*m*/*z* 413), the compound formed was the **2c** desaminated or, according Scheme 2, is derivative **4b**; In respect to

Table 1
Synthesis of novel imidazolidin-4-ones **2**–**5** produced by N^1-alkylation.

Entry	*n*	Method[a]	Yield %
2a	2	a	58.9
2b	3	a	49.4
2c	4	a	38.8
2d	4	b	–
3	–	a	37.4
4a	2	a	51.2
4b	3	a	38.4
5a	2	c	78.3
5b	3	c	85.3
5c	4	c	90.1

[a] Procedures are described in experimental section.