# Synthesis and characterization of analogues of the antimalarial alkaloid febrifugine

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# DECLARATION

I declare that this thesis is my own, unaided work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other university.

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# ABSTRACT

The subject of this thesis is the development of a potentially simple, general and economical synthetic protocol for the potent antimalarial alkaloid febrifugine (**1**) and its analogues. In Chapter 1, the interesting history of **1**, which includes a description of several reported total syntheses of **1**, is discussed. Natural products derived from **1**, as well as promising synthetic derivatives that display good antimalarial activity, are also discussed. The structure-activity relationships determined to date for **1** and its derivatives are presented in order to substantiate the need for the development of new synthetic strategies towards derivatives of **1** and its 3″-unsubstituted analogue, (±)-deoxyfebrifugine (**14**).

A brief overview of the general strategies used in the Organic Chemistry Group at the University of the Witwatersrand for the synthesis of alkaloids is given in Chapter 2. The Eschenmoser sulfide contraction reaction between a thiolactam and an α-bromocarbonyl compound results in the formation of a vinylogous amide (or "enaminone") product, which can be further manipulated to produce commonly encountered alkaloidal molecular skeletons. The chosen approach to **1** is based on reaction between the pivotal bromide 3-(3-bromo-2-oxopropyl)quinazolin-4(3*H*)-one (**105**) and suitable 3-substituted piperidine-2-thiones.

A series of model studies, described in Chapter 3, was performed in order to test the feasibility of the synthetic strategy. These studies resulted in a new preparation of the key bromide **105** and a new and efficient synthesis of (±)-deoxyfebrifugine (**14**). Enaminone analogues derived from five-, seven-, eight-, nine- and thirteen-membered thiolactams were also prepared for comparison. An interesting difference in the sensitivity of the five- and six-membered model cyclic vinylogous amides towards reducing agents was observed. Whereas three piperidine analogues of **14** could be prepared in high yields by the chemoselective hydrogenation of six-membered cyclic vinylogous amide precursors, the five-membered analogues either reacted non-selectively under various standard hydrogenation conditions, or resisted reduction entirely.

An extension of the approach towards the synthesis of a 3″-amino analogue of febrifugine (**1**) from L-ornithine is discussed in Chapter 4. Several 3-aminated piperidin-2-ones and thiones were prepared, but the subsequent enaminones were stable and characterizable only when the piperidinylidene ring nitrogen was alkylated. However, chemoselective reduction of the enaminone C=C bond in 3-{(*E*)-3-[(3*S*)-3-(*tert*-butoxycarbonylamino)-1-(4-methoxybenzyl)piperidin-2-ylidene]-2-oxopropyl}-quinazolin-4(3*H*)-one (**221**), an interesting 3-acylamino dehydro analogue of **1**, did not give the desired azafebrifugine, but instead yielded a 5,6,7,8-tetrahydro-1*H*-pyrido[3,2-*c*][1,2]oxazine derivative.

Several approaches to febrifugine (**1**) itself based on the successful model studies are discussed in Chapter 5. Initially, stereoselective α-bromination and subsequent substitution by oxygen of piperidin-2-ones derived from the chiral auxiliary (*S*)-phenylglycinol was explored. Unexpected racemization occurred at the α-position of the lactam during this route. A second approach to 3-hydroxypiperidin-2-one from L-arginine was also problematic. Finally, the utility of α-hydroxylation methodology (including Davis methodology) on *N*-substituted piperidin-2-ones was explored. This route yielded a range of 3-oxygenated lactams and thiolactams, many of which displayed optical activity. The crystal structures of several 3-substituted thiolactams were determined and compared. However, attempts to apply the sulfide contraction procedure to these precursors were unsuccessful.

Some investigations designed to explore the structural differences between vinylogous amides derived from the quinazoline-containing bromide **105** and thiolactams of different ring sizes are discussed in Chapter 6. Single crystal X-ray diffraction and NMR spectral data are compared for this series of compounds, the results revealing that the enaminone group in the five-membered ring derivative 3-[(3*Z*)-2-oxo-3-(pyrrolidin-2-ylidene)propyl]quinazolin-4(3*H*)-one **155** possesses a significantly different electronic distribution to the other analogues in the series.

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# ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| aq. | aqueous |
| Ar | aryl |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| Bu and *n*-Bu | butyl |
| *sec*-Bu | *sec*-butyl |
| $^t$Bu | *tert*-butyl |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| cat. | catalytic |
| CBz | benzyloxycarbonyl |
| conc. | concentration |
| *m*-CPBA | *m*-chloroperoxybenzoic acid |
| CS | (10-camphorsulfonyl)-oxaziridine |
| DBU | 1,8-diazabicyclo[5.4.0]-undec-7-ene |
| DCC | dicyclohexylcarbo-diimide |
| DCCS | (8,8-dichloro-10-camphorsulfonyl)-oxaziridine |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEPC | diethyl phosphoryl cyanide |
| DIBAL | diisobutylaluminium hydride |
| DMAP | 4-(*N,N*-dimethylamino)pyridine |
| DMF | *N,N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| E2 | bimolecular elimination |
| $EC_{50}$ | 50% effective concentration |
| EI | electron impact |
| El | electrophile |
| Et | ethyl |
| EtOAc | ethyl acetate |
| EWG | electron withdrawing group |
| FAB | fast atom bombardment |
| HMDO | hexamethyldisiloxane |
| HMDS | 1,1,1,3,3,3-hexamethyldisilazane |
| HPLC | high pressure liquid chromatography |
| HR | high resolution |
| IR | infrared |
| LAH | lithium aluminium hydride |
| LPS | lipopolysaccharide |
| Me | methyl |
| MOM | methoxymethyl |
| MoOPH | oxodiperoxymolyb-denum(pyridine)(hexa-methylphosphoric |

| | |
|---|---|
| | triamide) |
| MS | mass spectrometry |
| Ms | methanesulfonyl |
| NAP | 2-naphthylmethyl |
| NBS | *N*-bromosuccinimide |
| *l*-NMA | *N*-methyl-L-arginine |
| NOE | Nuclear Overhauser enhancement |
| Nu | nucleophile |
| o.n. | overnight |
| Pd/C | palladium on carbon |
| Ph | phenyl |
| PMB | *p*-methoxybenzyl |
| PPA | polyphosphoric acid |
| Pr | propyl |
| $^{i}$Pr and *i*-Pr | isopropyl |
| Q | quinazolin-2-yl |
| rt | room temperature |
| s.m. | starting material |
| $S_N1$ | unimolecular nucleophilic substitution |
| $S_N2$ | bimolecular nucleophilic substitution |
| TBDMS | *tert*-butyldimethylsilyl |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| Tf | trifluoromethane-sulfonyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| Ts | *p*-toluenesulfonyl |
| UV | ultraviolet |