

## ABSTRACT

Synthetic Studies Towards Conformationally Restricted Analogues of  
Caracasamide

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The hypotensive agent caracasamide, a metabolite of the plant *Verbesina caracasana*, has been used as the basis for the design of conformationally restricted analogues. Heterocyclic compounds, tetrahydropyridazine-1-carboximidamide **86** and tetrahydropyridazino[1,2-*a*][1,2,4]triazin-4(3*H*)-one **87** were conceived upon consideration of the *gauche* conformer of this naturally occurring guanidine. Additionally, a third structure, a tetrahydropyrimido[1,6-*c*][1,3,6]oxadiazepin-7-amine **105**, was designed using an intramolecular hydrogen-bonded conformation as a template. It was thought that preparation of these compounds would provide a means by which aspects of the pharmacodynamics of (*E*)-caracasamide could be probed. The synthetic effort towards these analogues, and the synthesis of (*E*)-caracasamide for conformational studies using NMR spectroscopy, are described in this thesis.

In Chapter 1, the metabolites of *V. caracasana* and other selected naturally occurring, bioactive guanidines are discussed. An overview of the pharmacology, synthesis and structure-activity relationships of (*E*)-caracasamide is also presented.

The use of conformationally restricted analogues and spectroscopy in the study of bioactive compounds for drug development is reviewed in Chapter 2, and the application of both techniques to the design of analogues of (*E*)-caracasamide is explored.

Chapter 3 features the synthesis of novel disubstituted hexahydropyridazines and a proposed mechanism for the unanticipated formation of urea and isourea derivatives, while the focus of Chapter 4 is the preparation of novel [1,2,4]triazinones *en route* to analogue **87**.

Chapter 5 describes preliminary attempts to prepare pyrimidine-4-carbonitriles, key intermediates in a proposed synthetic route to oxadiazepine **105**.

**Keywords:** Ainka Brown, caracasamide, conformational analogues, hexahydropyridazine, triazinone, oxadiazepine.