INTRODUCTION

Malaria continues to be a major cause of mortality and morbidity, especially in Sub-Saharan Africa. The emergence and spread of drug resistant parasites has highlighted the need for new chemically diverse, effective drugs. Historically, one of the major sources of antimalarial agents and novel template compounds has been higher order plants. A national multidisciplinary-consortium was established to scientifically investigate South African medicinal plants for the treatment of malaria. Over 134 plant taxa native to or naturalised in South Africa were selected and plant extracts thereof tested for in vitro activity against the D10 P. falciparum strain and cytotoxicity against Chinese Hamster Ovarian (CHO) cells.

METHODOLOGY

Plant material was collected from Middleburg in the Eastern Cape and extracted with dichloromethane. The crude extract was subjected to bio-assay guided fractionation using dichloromethane. The crude extract was subjected to bio-assay guided fractionation using 2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Compounds were characterised by NMR spectroscopy, mass spectrometry, X-ray crystallography and selected derivatisations.

RESULTS AND DISCUSSION

Five sesquiterpene lactones of the germacranolide and eudesmanolide type were isolated and identified, (Table 1, Compounds (1a) – (5)). Due to the marked instability of the germacranolide (1), the structural elucidation and bioassaying was conducted on the acetylated derivative (1a). Mosher’s method was applied to determine the absolute stereochemistry of the major compound (5), identifying it as (15,6R,7S,8S)-1,6-dihydroxy-4E,10(14),11(13)-germacratrien-12,8-olide. The reduction of the a-methylene group of compound (5) using NaBH4/MeOH yielded compound (6).

The germacranolides (1a), (4) and (5) showed equipotent antimalarial activity and were found to be significantly more active than the eudesmanolides (2) and (3). The antimalarial and cytotoxicity assay results of compound (6) clearly show that the C(11)-C(13) exocyclic double bond of compound (5) is primarily responsible for both the antimalarial activity and toxicity to CHO cells, as both are significantly decreased when this double bond is reduced.

CONCLUSION

None of the compounds was sufficiently active or selective to be a viable drug candidate but the potential for further structure-activity relationship (SAR) studies exists. The compounds could be used as scaffolds to generate lead molecules with enhanced antimalarial activity and reduced cytotoxicity. Further SAR work will also provide more insight into whether the observed antimalarial activity is due to biological activity or general cytotoxicity.

REFERENCES