Introduction

- Combretastatin A-4 (CA-4), a natural product stilbene is a potent microtubule-disrupting agent which binds at the colchicine-binding site of tubulin.
- The design, synthesis and biochemical evaluation of a series of analogues of the microtubule-stabilising agent CA-4 is described.
- The monocyclic β-lactam CA-4 analogues containing halogen substituents at the C-3 position of β-lactam ring were synthesized using the Staudinger reaction.
- Previous investigations described two approaches for the construction of 3-fluoro-β-lactams using the ketene-imine condensation and the enolate-imine condensation method.
- In the present work, the synthesis of 3-fluoro and 3,3-difluoro substituted β-lactams was developed easily by a convenient microwave assisted Reformatsky reaction using ethyl bromofluoroacetate and ethyl bromodifluoroacetate respectively (Scheme 1).

Results

- To the best of our knowledge, this is the first report of this new synthetic approach for 3-fluoro and 3,3-difluoro-β-lactams as CA-4 analogues.
- In the present work, the synthesis of 3-fluoro and 3,3-difluoro substituted β-lactams was developed easily by a convenient and applicable method using the Reformatsky reaction assisted by microwave using ethyl bromofluoroacetate and ethyl bromodifluoroacetate, respectively (scheme 1).
- All the 3-fluoro-1-8 and 3,3-difluoro 10-16 β-lactam compounds in this series contain 3,4,5-trimethoxyphenyl ring A with different substituents at phenyl ring B.
- The reaction was successful with short reaction time compared to the conventional Staudinger reaction, moderate yield and few steps required.

Xray Crystallographic Data m-fluorophenyl ring B β-lactams 6 & 14

- A preliminary screening was performed for all compounds in MCF-7 cells at two different concentrations: 1 µM and 10 µM.
- All the β-lactams are 80% viable remaining cells at 1 µM, except for compound 6 with 12.5 and 37% remaining at 10 µM and 1 µM respectively.

Anti-proliferative activities:

- A β-lactam with a large coupling constant of 4.21 Hz indicates that the only isomer present in the trans form. A doublet doublet signal appears at 0.499-5.02 ppm attributed to the proton at position 3 of the β-lactam with a large coupling constant of J<sub>2</sub>-7.1 Hz and 1.24 Hz due to the adjacent fluorine while H4 appears as doublet doublet at 5.18-5.31 ppm which is due to non-equivalent coupling of J<sub>2</sub>-2.24 and 1.86 Hz (H3 and F at C3).

Conclusion

- We have reported the ring closure of zinc enolate and imine with organozinc reagents in a one-pot fashion to form β-lactam. The required Reformatsky reagents were readily prepared by microwave irradiation TMCS with zinc in benzene for 5 min at 100 °C.
- Addition of this Reformatsky reagent to the corresponding bromoacetate and the relevant imine followed by further irradiation for 30 min at 100 °C provided the β-lactam in good yields.
- β-lactam 6 induced significant apoptosis in MCF-7 in dose and time dependent manner, and strongly inhibited tubulin assembly exhibiting activity at 3 fold greater than the control.

References


© Trinity College Dublin 2019. All rights reserved. This document may be reproduced for non-commercial, educational purposes, provided the source is acknowledged. For permission to reproduce for any other purpose, please email: melibaa@tcd.ie.