Exploring the mode of action of anti-leishmanial natural product analogues

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Abstract

The dehydrodieugenol family of natural products has specific activity against all *Leishmania* species tested.[1, 2] We have developed an active analogue with both cross-linking and click capabilities which allows access to various techniques for target identification including whole cell localisation and photo-affinity protein pull-downs. Using *L. mexicana* for our investigations, we demonstrate mitochondrial localisation using both fluorescence light microscopy and transmission electron microscopy.

The ascididemin family of natural products also shows promise as an antiparasitic, having activity against *P. falciparum* and various *Trypanosomes*,[3] although little is known about its mode of action. We have developed a range of analogues which are highly potent against *L. infantum*, *L. mexicana*, and *T. cruzi*. SAR knowledge from these analogues is a first step towards introducing a handle that can be used for bioorthogonal labelling. Additionally, this family shows metal ion binding capabilities which could contribute to compound mode of action.

Finally, we have explored the benzyltetrahydroisoquinoline alkaloids as antiparasitics. By synthesising a range of natural products and related analogues, we show good antiparasitic activity against *L. infantum*, *L. mexicana*, and *T. cruzi*.[4] We combine cell biology techniques such as monitoring cell cycle interruption, changed morphology and dsDNA damage to reveal that kinetoplast disruption likely plays a key role in the mode of action for this compound family.

These natural product families each have unique and varied chemical structures, allowing us to discover interesting and potentially novel modes of action against *Leishmania.*

References

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