POSTER PRESENTATION



Open Access

Acyclic nucleoside phosphonates containing a second phosphonate group are potent inhibitors of the 6-oxopurine phosphoribosyltransferases and have antimalarial activity

Dianne Keough¹, Petr Špaček², Dana Hocková², Tomáš Tichý², Silvie Vrbková², Lenka Slavětínská², Zlatko Janeba², Lieve Naesens³, Michael Edstein⁴, Marina Chavchich⁴, Tzu Wang^{1*}, John de Jersey¹, Luke Guddat¹

From Challanges in malaria research: Core science and innovation Oxford, UK. 22-24 September 2014

Background

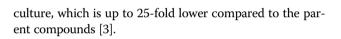
The 6-oxopurine phosphoribosyltransferases have been suggested to be a target for the discovery of new antimalarial drugs. This is because protozoan parasites rely solely on the salvage of purines from their host to make the nucleotides needed for RNA and DNA synthesis and lack the de novo pathway. Acyclic nucleoside phosphonates (ANPs) that contain a 6-oxopurine base are good inhibitors of the *Plasmodium falciparum* (Pf) and *Plasmodium vivax* (Pv) 6-oxopurine phosphoribosyltransferases (PRTs) [1]. Chemical modifications based on the crystal structure of 2-(phosphonoethoxy) ethylguanine (PEEG) in complex with human HGPRT have led to the design of new ANPs [2]. These novel compounds contain a second phosphonate group attached to the ANP scaffold [3].

Results

{[(2-[(Guanine-9Hyl)methyl]propane-1,3-diyl)bis(oxy)]bis (me thy-lene)} diphosphonic acid exhibited a K_i value of 30 nM for human HGPRT and 70 nM for Pf HGXPRT. The crystal structure of this compound in complex with human HGPRT shows that it fills or partially fills three critical locations in the active site: the binding sites of the purine base, the 5'-phosphate group, and pyrophosphate [3]. This is the first HG(X) PRT inhibitor that has been able to achieve this result. Pro-drugs have been synthesized resulting in IC₅₀ values as low as 3.8 μ M for Pf grown in cell

¹School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, Queensland, Australia

Full list of author information is available at the end of the article



Conclusion

The crystal structure of {[(2-[(Guanine-9Hyl)methyl] propane-1,3-diyl)bis(oxy)]bis(methylene)} diphosphonic acid in complex with human HGPRT provides a template for chemical modifications to increase both potency and selectivity for the parasite enzymes.

Acknowledgements

This work was financially supported by Australia National Health and Medical Research Council (Grants 569703 and 1030353), the Grant Agency of Czech Republic (Grant P207/11/0108) and Gilead Sciences (Foster city, CA).

Authors' details

¹School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, Queensland, Australia. ²Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague, Czech Republic. ³Rega Institue for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium. ⁴Australia Army Malaria Institute, Brisbane, Queensland, Australia.

Published: 22 September 2014

References

- Hockova D, Holy A, Masojidkova M, Keough DT, de Jersey J, Guddat LW: Synthesis of branched 9-[2-(2-phosphonoethoxy)ethyl]purines as a new class of acyclic nucleoside phosphonates which inhibit Plasmodium falciparum hypoxanthine-guanine-xanthine phosphoribosyltransferase. *Bioorg Med Chem* 2009, 17:6218-6232.
- Keough DT, Hockova D, Holy A, Naesens LM, Skinner-Adams TS, Jersey J, Guddat LW: Inhibition of hypoxanthine-guanine phosphoribosyltransferase by acyclic nucleoside phosphonates: a new class of antimalarial therapeutics. J Med Chem 2009, 52:4391-4399.
- 3. Keough DT, Spacek P, Hockova D, *et al*: Acyclic nucleoside phosphonates containing a second phosphonate group are potent inhibitors of



© 2014 Keough et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The Creative Commons Public Domain Dedication waiver (http:// creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

6-oxopurine phosphoribosyltransferases and have antimalarial activity. *J Med Chem* 2013, 56:2513-2526.

doi:10.1186/1475-2875-13-S1-P91

Cite this article as: Keough *et al.*: Acyclic nucleoside phosphonates containing a second phosphonate group are potent inhibitors of the 6-oxopurine phosphoribosyltransferases and have antimalarial activity. *Malaria Journal* 2014 **13**(Suppl 1):P91.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar

BioMed Central

• Research which is freely available for redistribution

Submit your manuscript at www.biomedcentral.com/submit