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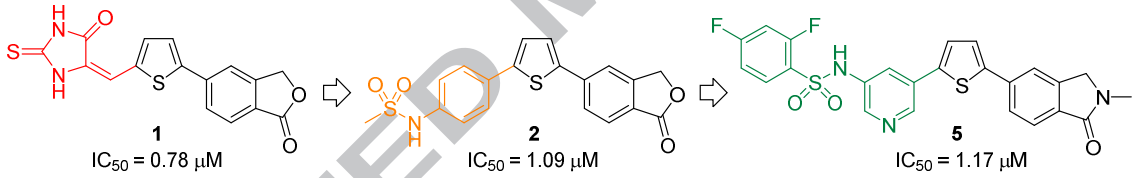
Benzenesulphonamide inhibitors of the cytolytic protein perforin

Julie A. Spicer[a,b,*], Christian K. Miller[a,b], Patrick D. O'Connor[a,b], Jiney Jose[a,b], Kristiina M. Huttunen[a,c], Jagdish K. Jaiswal[a,b], William A. Denny[a,b], Hedieh Akhlaghi[d], Kylie A. Browne[d], Joseph A. Trapani[d,e]

[a]*Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.*
[b]*Maurice Wilkins Centre for Molecular Biodiscovery, A New Zealand Centre for Research Excellence, Auckland, New Zealand.*
[c]*School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, P.O. Box 1627, FI-70211 Kuopio, Finland.*
[d]*Cancer Immunology Program, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Victoria 3000, Australia.*
[e]*Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Victoria 3052 Australia.*

Keywords
Perforin; Perforin inhibitor; Benzenesulphonamide; Bioisostere; Immunosuppressant

Graphical Abstract



Abstract
The pore-forming protein perforin is a key component of mammalian cell-mediated immunity and essential to the pathway that allows elimination of virus-infected and transformed cells. Perforin activity has also been implicated in certain auto-immune conditions and therapy-induced conditions such as allograft rejection and graft versus host disease. An inhibitor of perforin activity could be used as a highly specific immunosuppressive treatment for these conditions, with reduced side-effects compared to currently accepted therapies. Previously identified first-in-class inhibitors based on a 2-thioxoimidazolidin-4-one core show suboptimal physicochemical properties and toxicity toward the natural killer (NK) cells that secrete perforin *in vivo*. The current benzenesulphonamide-based series delivers a non-toxic bioisosteric replacement possessing improved solubility.

The primary role of cytotoxic T lymphocytes (CTL) and NK cells is to eliminate virally infected or oncogenic target cells.[1] This process takes place *via* the granule exocytosis pathway[2] where, upon stable conjugation with a target cell, the contents of cytotoxic granules contained in CTL or NK cells are secreted into the synaptic cleft formed between effector and