Invited Article

Screening of the ‘Pathogen Box’ identifies an approved pesticide with major anthelmintic activity against the barber's pole worm

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Abstract

There is a substantial need to develop new medicines against parasitic diseases via public-private partnerships. Based on high throughput phenotypic screens of largely protozoal pathogens and bacteria, the Medicines for Malaria Venture (MMV) has recently assembled an open-access ‘Pathogen Box’ containing 400 well-curated chemical compounds. In the present study, we tested these compounds for activity against parasitic stages of the nematode Haemonchus contortus (barber’s pole worm). In an optimised, whole-organism screening assay, using exsheathed third-stage (xL3) and fourth-stage (L4) larvae, we measured the inhibition of larval motility, growth and development of H. contortus. We also studied the effect of the ‘hit’ compound on mitochondrial function by measuring oxygen consumption. Among the 400 Pathogen Box compounds, we identified one chemical, called tolfenpyrad (compound identification code: MMV688934) that reproducibly inhibits xL3 motility as well as L4 motility, growth and development, with IC50 values ranging between 0.02 and 3 μM. An assessment of mitochondrial function showed that xL3s treated with tolfenpyrad consumed significantly less oxygen than untreated xL3s, which was consistent with specific inhibition of complex 1 of the respiratory electron transport chain in arthropods. Given that tolfenpyrad was developed as a pesticide and has already been tested for absorption, distribution, excretion, biotransformation, toxicity and metabolism, it shows considerable promise for hit-to-lead optimisation and/or repurposing for use against H. contortus and other parasitic nematodes. Future work should assess its activity against hookworms and other pathogens that cause neglected tropical diseases.

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1. Introduction

Compounded by massive global food and water shortages and climate change, parasitic illnesses, including neglected tropical diseases (NTDs; WHO, 2015), have a devastating, long-term impact on human and animal health and welfare worldwide, and thus represent a major global challenge. Together, NTDs infect more than one billion people worldwide, resulting in an estimated loss of 26 million disability-adjusted life years (Hotez et al., 2014).

Despite their adverse socioeconomic impact, there are major limitations in the diagnosis, treatment and control of NTDs. Currently, there are no commercial vaccines available against most of these diseases (Pedrique et al., 2013; Hotez et al., 2016), diagnostic methods frequently suffer from insufficient specificity and sensitivity (Utzinger et al., 2012; Assefa et al., 2014), and treatments are often not highly effective and/or are toxic (Castro et al., 2006; Witschel et al., 2012; Molina et al., 2015). In addition, often the small numbers of drugs (or drug classes) frequently used, limited use of combination drug therapies and the implementation of mass drug administration programs bear the risk of drug resistance emerging in some groups of target pathogens (Humphries et al., 2012; Witschel et al., 2012; Webster et al., 2014). Therefore, the development of new drugs is crucial to ensure effective and sustained treatment and control into the future.

In spite of some success through the discovery of, for example, monepantel (Kaminsky et al., 2008; Prichard and Geary, 2008) and derquantel (Little et al., 2011), progress in discovering new drugs against parasitic worms of animal health importance has been relatively poor. Likely reasons for limited success beyond the lack of resources include an over-confidence in the validation of molecular targets (enzymes and receptors) and in studying an inappropriate developmental stage of a pathogen. However, key gaps include a lack of readily available curated sets of compounds for targeted screening and subsequent evaluation, limited cooperation among different areas (including parasitology, drug discovery, medicinal chemistry and safety evaluation) which are essential to find starting points for drug discovery, and to bring them to tangible and translational outcomes and outputs.

In the late 1990s, an innovative collaboration model for research and development for neglected diseases emerged in the form of public-private partnerships (PPPs) that came to be known as product development partnerships (PDPs). A key example is the Medicines for Malaria Venture (MMV), created from a desire to catalyse the discovery development and delivery of new medicines against malaria. Over the last decade, almost seven million compounds have been tested in phenotypic assays against malaria, and this has resulted in a solid pipeline of new preclinical and clinical candidates. In addition, an open science initiative has made many of these structures available, and a collection of 400 key malaria phenotypic ‘hits’, called the ‘Malaria Box’, was launched in 2013. Building on this model, in December 2015, MMV took this a stage further, with an initiative to stimulate the discovery of drugs for neglected parasitic diseases. The ‘Pathogen Box’ (www.pathogenbox.org), contains 400 diverse drug-like molecules, and is provided at no cost to research groups.

Each of the 400 compounds in the ‘Pathogen Box’ has confirmed activity against one or more key pathogens that cause some of the most socioeconomically important diseases worldwide, including tuberculosis, malaria, sleeping sickness, leishmaniasis, schistosomiasis, hookworm disease, toxoplasmosis and cryptosporidiosis. In addition, all compounds have been tested for cytotoxicity, with compounds included in the library being at least 5-fold more selective for the pathogen than its mammalian host. The complete set of compounds is dispatched to laboratories around the world to boost drug discovery efforts. This initiative provided us with a unique opportunity to assess these curated compounds for nematocidal activity in a recently developed whole-organism screening assay (Preston et al., 2015, 2016). Our aim was to rapidly screen all 400 compounds against parasitic stages of the barber’s pole worm, Haemonchus contortus, and to identify hit compounds and characterise/assess them for further evaluation as nematocidal candidates. This worm was used because it is one of the best-studied members of a large order (Strongyloida) of socioeconomically important nematodes of animals, including humans, because there is extensive information available on its biology and molecular biology, and because its genome and developmental transcriptome have been characterised in detail (Gasser and von Samson-Himmelstjerna, 2016), providing a foundation for drug discovery efforts.

2. Materials and methods

2.1. Procurement of H. contortus

The Haeeon-5 strain of Haemonchus contortus, which is partially resistant to benzimidazoles (Dr Jody Zawadzki, personal communication), was maintained in experimental sheep as described previously (Schwarz et al., 2013; Preston et al., 2015) and in accordance with the institutional animal ethics guidelines (permit no. 1413429; The University of Melbourne, Australia). L3s were produced from H. contortus eggs by incubating faeces from infected sheep at 27 °C for 1 week (Preston et al., 2015), sieved through nylon mesh (pore size: 20 μm) to remove debris or dead larvae and then stored at 10 °C for a maximum of 3 months. For screening and basal oxygen consumption measurements (see following subsections), L3s were exsiccated and sterilised in 0.15% v/v sodium hypochlorite (NaClO) at 37 °C for 20 min (Preston et al., 2015). Thereafter, Xl3s were washed five times in sterile physiological saline by centrifugation at 600 g (5 min) at 22–24 °C. Then, Xl3s were immediately suspended in Luria Bertani medium [LB: 10 g of tryptone (cat no. LP0042; Oxoid, England), 5 g of yeast extract (cat no. LP0042; Oxoid) and 5 g of NaCl (cat. no. K4320804210; Merck, Denmark)] in 1 l of reverse-osmosis deionised water. LB was autoclaved and supplemented with 100 IU/ml of penicillin, 100 μg/ml of streptomycin and 2.5 μg/ml of amphotericin (Fungizone, antibiotic – antifungal; cat. no. 15240-062; Gibco, USA); this supplemented LB was designated LB*. Fourth-stage larvae (L4s) were produced from Xl3s in vitro for 7 days at 38 °C and 10% CO2, as described by Preston et al. (2015, 2016).
2.2. Screening of compounds

The Pathogen Box contains 400 compounds representing compounds that are active against one or more of 12 distinct pathogens (http://www.pathogenbox.org/about-pathogen-box/supporting-information). Individual compounds had only been tested to confirm activity against the pathogen for which the compounds were first reported to be active, and have not been tested against the other pathogens represented in the Pathogen Box. All compounds have been tested for cytotoxicity; typically, they are five-fold less potent against a human fibroblast cell line (MRC-5) than the pathogen (cf. Table 1); toxicity values are within levels considered acceptable for an initial drug discovery programme (www.pathogenbox.org/about-pathogen-box/supporting-information). Each of the 400 compounds was prepared as described previously (Preston et al., 2015) and screened (in triplicate) at a concentration of 20 μM on X3 of H. contortus in 96-well microculture plates using two reference-control compounds, moxidectin and monepantel (Preston et al., 2015, 2016). In brief, compounds were dissolved to a stock concentration of 10 mM in dimethyl sulfoxide (DMSO, Ajax Finechem, Australia). Compounds were individually diluted to the stock concentration of 10 mM in dimethyl sulfoxide (DMSO, Ajax Finechem, Australia). Compounds were dissolved to the final concentration of 20 μM using LB*, and dispensed (in triplicate) into wells of the microculture plates using a multichannel pipette. In addition, the negative-controls (LB* and LB* + 0.5% DMSO; six wells each), and positive-controls (final concentration of 20 μM of monepantel [Zolvix, Novartis Animal Health, Switzerland] and 20 μM of moxidectin [cydectin, Virbac, France]) were dispensed in triplicate wells. Then, X3s (~300/well) were dispensed into wells of the plate using an automated multichannel pipette (Vialflow Assist/II, Integra Biosciences, Switzerland). Following an incubation for 72 h at 38 °C and 10% CO2, a video recording (5 s) was taken of each well of the 96-well microculture plate (containing X3s) using a grey-scale camera (Rolera bolt, Q imaging Scientific Coms, Canada), and a motorised X-Y axis stage (BioPoint 2, Ludl Electronics Products, USA). Individual videos were processed to calculate a motility index (MI) using an algorithm described previously (Preston et al., 2015, 2016). MIs were normalised to the positive- and negative-controls (to remove plate-to-plate variation) using the program Prism (v.6 GraphPad Software, USA). A compound was recorded as having activity if it reduced X3 motility by ≥ 70% after 72 h of incubation.

2.3. Dose-response assessments of active compounds on X3 and L4 motility, and L4 growth and development

Anti-X3 activity of any ‘hit’ compound was confirmed, and half maximum inhibitory concentration (IC50) values estimated from dose-response curves (24 h, 48 h and 72 h). Compounds that reduced the motility of X3s were also tested for their ability to inhibit the development of X3s to L4s, the motility of L4s and/or their ability to retard L4 growth, as described previously (Preston et al., 2015, 2016). In brief, growth retardation and morphological alterations in L4s exposed for 48 h to LB* containing either 1% DMSO (negative-control), 100 μM of each tolfenpyrad (test compound), moxidectin (positive-control) or monepantel (positive-control) were assessed microscopically (20–100 × magnification). For each treatment, the mean width of 30 L4s ± the standard error of the mean (SEM) was calculated, and a non-parametric (Kruskal-Wallis) one-way ANOVA and Dunn’s multiple comparison test was used to calculate statistical difference between treatments. All assays (X3 motility, and L4 development, growth and motility) were performed in triplicate, between 3 and 5 times on different days. To determine IC50 values, the data from each assay (X3 motility, L4 motility and development) were converted to a percentage with reference to the negative-control (LB* + 0.5% DMSO), and IC50 values determined using a variable slope four-parameter equation, constraining the top value to 100% and using a least squares (ordinary) fit model (v.6 GraphPad Software). Selectivity indices (SIs) were calculated using a recognised formula (SI = human fibroblast (MRC-5) cells IC50/H. contortus IC50; Fisher et al., 2014) employing cytotoxicity data linked to the Pathogen Box compounds.

2.4. Measurement of basal oxygen consumption

Following standardization using an established protocol, the basal oxygen consumption (respiratory) rate in X3s was measured using the Seahorse XF24 flux analyser (Seahorse Biosciences, USA) (McGee et al., 2011). In brief, 450 μl of LB* + 1% DMSO containing 100 μM of tolfenpyrad (‘hit’ compound) or 100 μM of moxidectin (control; not known to inhibit respiration), or LB* + 1% DMSO alone (untreated control) were transferred in quadruplicate to the wells of a 24-well plate (Seahorse XF24). Then, 1000 X3s in 50 μl LB* were added to the wells, and the plates pre-incubated for 2 h, equilibrated for 30 min and oxygen consumption measured using the flux analyser. Seven measurements were taken over a 1 h-period (protocol: 2 min-mix, 2 min-pause and 4 min-measure; McGee et al., 2011). Experiments were repeated twice. A two-way repeated measures ANOVA with a Dunnett’s multiple comparison test (v.6 GraphPad Prism) was used to assess the statistical difference in oxygen consumption between treated and untreated X3s.

3. Results

In the primary screen of the 400 compounds (Fig. 1; Supplementary file 1), one compound (tolfenpyrad; Compound ID: MMV688934; batch: MMV688934-01; pubchem.ncbi.nlm.nih.gov/compound/10110536) was recorded to inhibit X3 motility by ≥ 70%. Although there are benzimidazole-based compounds in the Pathogen Box, nematocidal activity was not detected using this >70% threshold, because the Haecon-5 strain of H. contortus is partially resistant to this class of chemicals. Subsequent assays using X3s and L4s of H. contortus showed that the potency of tolfenpyrad, measured as IC50 values, ranged from 0.02 to 3 μM (Fig. 1; Table 1). In comparison to moxidectin and monepantel, tolfenpyrad was able to reduce motility earlier than monepantel, with inhibition occurring after 2 h of exposure and an IC50 value of 2.3 μM for monepantel (Fig. 3). Tolfenpyrad and monepantel were found to have a similar inhibitory effect on X3 motility at the time points tested (Table 1). Furthermore, when examining the inhibitory activity of the compounds on L4 motility, tolfenpyrad and monepantel had lower IC50 values at 24 h, 48 h and 72 h compared with that of monepantel (Table 1). In the L4 development assay, tolfenpyrad had a greater inhibitory effect on the development of X3 to L4 (IC50 of 0.06 μM) than did moxidectin and monepantel (IC50 of 12.3 μM and 0.4 μM, respectively). Light microscopic examination of parasitic larvae revealed morphological damage (shriveled and granulated appearance) in L4s following exposure in vitro (48 h) to tolfenpyrad and monepantel (Fig. 2), but not in X3s (data not shown). L4s exposed to tolfenpyrad were significantly thinner than ‘untreated’ controls, and had a similar width to moxidectin-exposed, but not as pronounced as monepantel-exposed larvae (Fig. 2). Finally, it was assessed whether tolfenpyrad would inhibit respiration in H. contortus X3s, as it does in arthropods by targeting complex I of the respiratory electron transport chain (Song et al., 2013), by measuring oxygen consumption over time (Fig. 3). The results showed that tolfenpyrad-treated X3s consumed substantially (P < 0.05) less oxygen than both moxidectin-treated and untreated X3s (Fig. 3) (Table 1).
4. Discussion

The screening of the Pathogen Box compounds identified one chemical, tolfenpyrad, with major activity against parasitic larval stages (xL3 and L4) of *H. contortus* *in vitro*; IC_{50} values were comparable with those of two commercially available anthelmintics, monepantel and moxidectin, as well as cytotoxicity data for tolfenpyrad.

| Bioassay          | Time   | IC_{50} (μM) Tolfenpyrad | Monepantel | Moxidectin |
|-------------------|--------|--------------------------|------------|------------|
| xL3 motility      | 24 h   | 2.3                      | 5.2        | 2.5        |
|                   | 48 h   | 3.0                      | 6.0        | 2.5        |
|                   | 72 h   | 3.0                      | 0.4        | 2.3        |
| L4 development    | 7 days | 0.06                     | 0.4        | 12.3       |
| L4 motility       | 24 h   | 0.13                     | 4.3        | 2.2        |
|                   | 48 h   | 0.06                     | 2.2        | 0.6        |
|                   | 72 h   | 0.02                     | 3          | 0.005      |
| Cytotoxicity      |        | 56                       | na         | na         |

* Data from the Laboratory of Microbiology, Parasitology and Hygiene (LMPH), University of Antwerp, provided to Medicines for Malaria Venture (MMV) to accompany the Pathogen Box. na = not applicable.

Fig. 1. The ‘Pathogen Box’ from the Medicines for Malaria Venture (MMV) (Panel A) contains 400 diverse drug-like molecules with confirmed activity against one or more key pathogens that cause some of the most socioeconomically important diseases worldwide, including malaria, toxoplasmosis, cryptosporidiosis, trypanosomiasis, leishmaniasis, hookworm disease, trichuriasis, schistosomiasis; numbers of chemicals active against different pathogen/pathogen groups are indicated in parentheses. The graphs (Panels B to D) show the activity of tolfenpyrad on the motility of exsheathed third-stage (xL3) and fourth-stage (L4) larvae of *Haemonchus contortus* (after 24 h, 48 h and 72 h of exposure) and on the development of the L4 stage (after 7 days of exposure), respectively.
of complex I of the respiratory electron transport chain in mitochondria (Lummen, 1998; Song et al., 2013), such that it is effective against various pests that are resistant to insecticides, including organophosphates and carbamates, which have modes of action that are entirely distinct from tolfenpyrad.

To explore whether tolfenpyrad might act as an inhibitor of the electron transport chain in *H. contortus*, oxygen consumption was measured in xL3s in the presence or absence of tolfenpyrad following a pre-exposure for 2 h to the compound. This approach is routinely used to evaluate mitochondrial function in *Caenorhabditis elegans* and mammalian tissue by detecting oxygen consumption in real-time using oxygen-sensitive probes (McGee et al., 2011; Andreux et al., 2014). In the present study, we elected to pre-treat xL3s of *H. contortus* for 2 h prior to the initial measurement of oxygen consumption, as both tolfenpyrad and moxidectin significantly inhibit motility following acute exposure. The results revealed a significant decrease in oxygen consumption in xL3s exposed to tolfenpyrad compared with untreated controls. Similarly, oxygen consumption was lower in tolfenpyrad-treated than moxidectin-treated xL3s, which was also associated with reduced motility following the exposure for 2 h. This discrepancy in oxygen consumption between these treatments indicates that tolfenpyrad is also most likely acting as a complex I mitochondrial electron transport inhibitor in *H. contortus*.

Although mainly used against agricultural pests, tolfenpyrad had not been assessed previously for use against endoparasites, such as parasitic worms, of animals. A report was prepared by the Joint FAO/WHO Meeting on Pesticide Residues at the request of the Codex Committee on Pesticide Residues in 2013 (FAO, 2013). This report extensively reviewed and appraised many aspects of tolfenpyrad, including: (i) acceptable daily intake; (ii) absorption, distribution, excretion and biotransformation; (iii) toxicity studies (acute; short and long-term; carcinogenicity; genotoxicity; reproductive, developmental and neural toxicity), and (iv) studies of metabolites. The main conclusions from this report were: (i) the acceptable daily intake of tolfenpyrad is 0–0.006 mg/kg in mammals; (ii) following oral administration, tolfenpyrad is rapidly absorbed, widely distributed and metabolized by the liver, with 88–93% being excreted in the faeces, and (iii) tolfenpyrad was not found to be carcinogenic, genotoxic or neurotoxic, but was found to have some reproductive and developmental toxicity. Although some intoxications (associated with excessive exposure/ingestion) have been recorded in humans (e.g., Yamaguchi et al., 2012; Hikiji et al., 2013), well-controlled risk assessment studies in...
monogastric mammals (mouse, rat, rabbit and dog) have shown that the no-observed-adverse-effect levels (NOAELs) of tolfenpyrad are between 1 and 1.5 mg/kg body weight per day, with lowest-observed-adverse-effect levels (LOAEL) of 5–21 mg/kg body weight per day (FAO, 2013). Therefore, based on the evidence presented in this report and associated literature (see FAO, 2013) as well as the high selectivity of tolfenpyrad for *H. contortus* and/or related parasitic nematodes at dosages between 1 and 5 mg/kg body weight. We also propose to assess its activity in *in vitro* against the hookworms *Ankylostoma ceylanicum* and *Necator americanus* of humans and other NTD pathogens (London Declaration, 2012). Nonetheless, it will be important to also extend medicinal chemistry work to establish whether a safer and more effective derivative of this chemical might be synthesized. Given that tolfenpyrad was developed as a pesticide and has already been tested for absorption, distribution, excretion, biotransformation, toxicity and metabolism, there is considerable promise for the repurposing of this chemical for use against *H. contortus* and other parasitic nematodes. Further work should now focus on assessing the activity of tolfenpyrad against hookworms and other worms that cause NTDs.

**Conflicts of interest**

The authors declare no conflicts of interest.

**Acknowledgements**

The present study was funded by the National Health and Medical Research Council of Australia (NHMRC), the Australian Research Council (ARC) and the Wellcome Trust (RGB), and supported by a Victoria Life Sciences Computation Initiative, Australia (VLSI; grant no. VR0007) on its Peak Computing Facility at The University of Melbourne, Australia, an initiative of the Victorian Government, Australia. Animal ethics approval (AEC no. 0707258) was granted by The University of Melbourne. We thank our colleagues at MMV, especially Angelique Doy, for their support.

**Appendix A. Supplementary data**

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ijpddr.2016.07.004.

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Accepted 19 03 2016.

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Author/s: Preston, S; Jiao, Y; Jabbar, A; McGee, SL; Laleu, B; Willis, P; Wells, TNC; Gasser, RB

Title: Screening of the 'Pathogen Box' identifies an approved pesticide with major anthelmintic activity against the barber's pole worm

Date: 2016-12-01

Citation: Preston, S., Jiao, Y., Jabbar, A., McGee, S. L., Laleu, B., Willis, P., Wells, T. N. C. & Gasser, R. B. (2016). Screening of the 'Pathogen Box' identifies an approved pesticide with major anthelmintic activity against the barber's pole worm. INTERNATIONAL JOURNAL FOR PARASITOLOGY-DRUGS AND DRUG RESISTANCE, 6 (3), pp.329-334. https://doi.org/10.1016/j.ijpddr.2016.07.004.

Persistent Link: http://hdl.handle.net/11343/123253

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