Accepted Manuscript

Progress in Antischistosomal *N,N'*-Diarylurea SAR

Jianbo Wu, Chunkai Wang, Derek Leas, Mireille Vargas, Karen L. White, David M. Shackleford, Gong Chen, Austin G. Sanford, Ryan M. Hemsley, Paul H. Davis, Yuxiang Dong, Susan A. Charman, Jennifer Keiser, Jonathan L. Vennerstrom
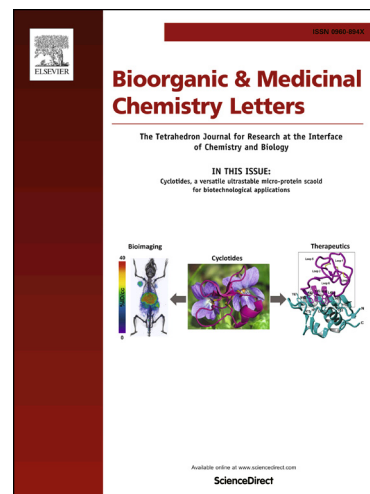
Graphical Abstract

MMV665852
LogP 5.2, sol. <1.6 μg/mL
S. mansoni IC$_{50}$ 0.80 μM
S. mansoni WBR 0%
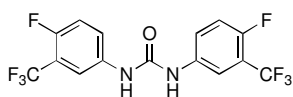
1
LogP 4.5, sol. <1.6 μg/mL
S. mansoni IC$_{50}$ 0.19 μM
S. mansoni WBR 40%
AUC$_{0\text{-last}}$ 394 μM.h
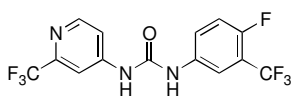
18
LogP 3.8, sol. 3.1-6.3 μg/mL
S. mansoni IC$_{50}$ 0.66 μM
S. mansoni WBR 50%
AUC$_{0\text{-last}}$ 1,486 μM.h

Progress in Antischistosomal *N,N′*-Diarylurea SAR

Jianbo Wu[a], Chunkai Wang[a], Derek Leas[a], Mireille Vargas[b,c], Karen L. White[d], David M. Shackleford[d], Gong Chen[d], Austin G. Sanford[e], Ryan M. Hemsley[e], Paul H. Davis[e], Yuxiang Dong[a], Susan A. Charman[d], Jennifer Keiser[b,c], Jonathan L. Vennerstrom[a*]

[a]College of Pharmacy, University of Nebraska Medical Center, 986025 Nebraska Medical Center, Omaha, NE, United States

[b]Department of Medical Parasitology and Infection Biology, Swiss Tropical Institute, Socinstrasse 57, CH-4002 Basel, Switzerland

[c]University of Basel, CH-4003 Basel, Switzerland

[d]Centre for Drug Candidate Optimisation, Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia

[e]Department of Biology, University of Nebraska at Omaha, Omaha, NE, United States

tel: 402.559.5362

fax: 402.559.9543

email: jvenners@unmc.edu

Abstract

N,N'-diarylureas have recently emerged as a new antischistosomal chemotype. We now describe physicochemical profiling, *in vitro* ADME, plasma exposure, and *ex vivo* and *in vivo* activities against *Schistosoma mansoni* for twenty new *N,N'*-diarylureas designed primarily to increase aqueous solubility, but also to maximize structural diversity. Replacement of one of the 4-fluoro-3-trifluoromethylphenyl substructures of lead *N,N'*-diarylurea **1** with azaheterocycles and benzoic acids, benzamides, or benzonitriles decreased lipophilicity, and in most cases, increased aqueous solubility. There was no clear relationship between lipophilicity and metabolic stability, although all compounds with 3-trifluoromethyl-4-pyridyl substructures were metabolically stable. *N,N'*-diaryl ureas containing 4-fluoro-3-trifluoromethylphenyl, 3-trifluoromethyl-4-pyridyl, 2,2-difluorobenzodioxole, or 4-benzonitrile substructures had high activity against *ex vivo S. mansoni* and relatively low cytotoxicity. *N,N*-diaryl ureas with 3-trifluoromethyl-4-pyridyl and 2,2-difluorobenzodioxole substructures had the highest exposures whereas those with 4-fluoro-3-trifluoromethylphenyl substructures had the best *in vivo* antischistosomal activities. There was no direct correlation between compound exposure and *in vivo* activity.

Keywords: *N,N'*-diarylurea, antischistosomal, SAR

Schistosomiasis is a widespread tropical parasitic disease[1]; *Schistosoma mansoni*, *S. haematobium* and *S. japonicum* are the predominant pathogenic species.[2-4] Praziquantel is the only drug used for treatment of schistosomiasis. Even so, praziquantel drug resistance is not yet widespread.[4-7] We thus have a window of opportunity to identify a new antischistosomal drug. In this regard, several antischistosomal lead compounds have recently been identified by phenotypic screening of drug and chemical compound libraries.[8-11] One of these was the symmetrical *N,N'*-diaryl urea MMV665582,[9] a structural analog of triclocarban,[12,13] an antibacterial agent used in detergents, cosmetics, and other products (Figure 1).

MMV665852, X = Cl
Triclocarban, X = H
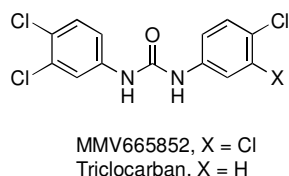
Figure 1.

With an IC_{50} of 0.8 μM, MMV665852 is only 4-fold less potent than praziquantel against *ex vivo S. mansoni* and has a 64-fold in vitro selectivity index. A single 400 mg/kg oral dose of MMV665852 administered to *S. mansoni*-infected mice reduced worm burden by 53%. In an initial pharmacokinetic investigation of MMV665852, this symmetrical *N,N'*-diarylurea was characterized by a half-life of 4.7 h and C_{max} of 4.4 μM at a 46.3 mg/kg oral dose.[9] Thus, this very simple compound offers intriguing possibilities for further optimization, although this is tempered by its high Log P of 5.2, and the low aqueous solubility[14] and potential pharmacological promiscuity[12,13,15,16] of this compound class. Following the discovery of MMV665852, two subsequent studies[17,18] established an initial SAR for this compound series: 1) substitution at positions 3 and 4 of the phenyl rings with H, F, Cl, CN, and CF_3 groups was optimal; 2) substitution at positions 3 and 4 of the phenyl rings with OCH_3, NH_2 and other

4

electron-donating groups diminished activity; 3) replacement of one of the phenyl rings with alkyl substituents diminished or abolished activity; 4) cyclization of the urea to imidazoline-2-ones abolished activity; and 5) replacement of the urea with carbamates, thioureas, sulfonamides, or oxalamides diminished or abolished activity. Concurrent with this work, we found that the symmetrical *N,N'*-diarylurea **1**,[19] a side-reaction product formed in the synthesis of aryl hydantoins,[20] had promising antischistosomal activity, better than that of MMV665582. We now describe physicochemical profiling, *in vitro* ADME, plasma exposure, and *ex vivo* and *in vivo* activities against *S. mansoni* for a number of analogs of **1** (**2**-**20**, Table 1) designed primarily to increase aqueous solubility, but also to maximize structural diversity.

Target *N,N'*-diarylureas **2** and **6**-**20** were prepared (Supporting Information) by reactions of phenyl isocyanates (Table 1 Ar = a, d, l, n) with the requisite anilines under three slightly different reaction conditions (Scheme 1). Phenyl isocyanates were prepared in situ by treatment of the precursor anilines with triphosgene. Target *N,N'*-diarylureas **3**,[21] **4**,[22] and **5** were prepared by treatment of the corresponding anilines with 1,1'-carbonyldiimidazole (CDI) (Scheme 1).
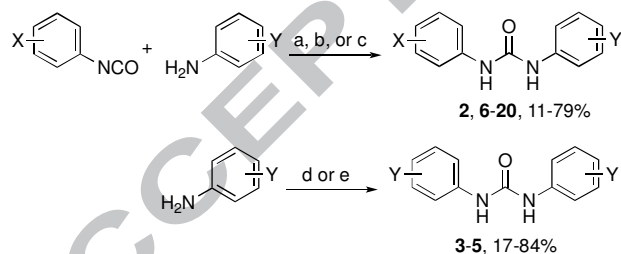
Scheme 1. Reagents and conditions: (a) *N,N*-diisopropylethylamine, CH$_2$Cl$_2$, rt, 12 h (**2**, **17**, **18**); (b) THF, 25-80 °C; 12 h (**6**-**9**, **19**, **20**); (c) CH$_3$CN, 80 °C, 12 h (**10**-**16**); (d) CDI, THF, rt, 48 h (**3**, **4**); (e) CDI, 1,2-dimethoxyethane, reflux, 16 h (**5**).

We first consider the physicochemical and *in vitro* ADME properties of these analogs of **1** (Table 1). The calculated polar surface area (PSA) values of between 41 and 93 Å^2 indicate that

the polarity of these compounds is unlikely to be a rate-limiting factor for membrane permeability and oral bioavailability.[23] Symmetrical *N,N*-diaryl urea **1** had a high $LogD_{7.4}$ of 4.5, similar to that of 5.2 for MMV665852,[9] and its kinetic solubility was very poor (<1.6 µg/mL). The symmetrical azaheterocycle *N,N*-diaryl ureas **2**, **3**, and **4** were considerably more polar and more soluble at both pH 2 and 6.5 compared to **1**. In contrast, the symmetrical 2,2-difluorobenzodioxole *N,N*-diaryl urea **5** had a similar $LogD_{7.4}$ to that of **1** and was not more soluble.

Table 1. Physicochemical and *in vitro* ADME properties for *N,N'*-diarylureas **1**-**20**.
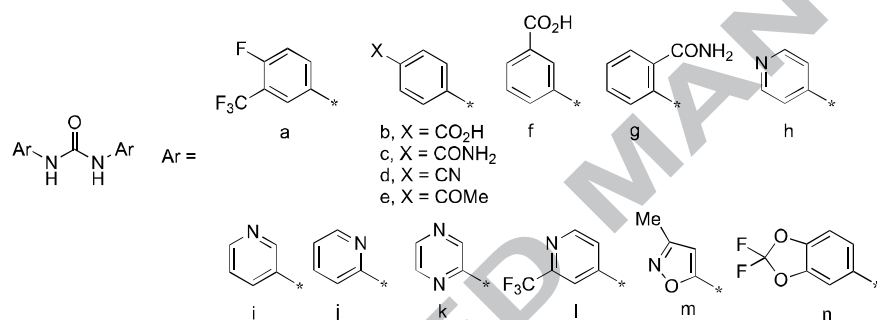
Compd	Ar	$LogD_{7.4}$[a]	PSA (Å^2)[b]	$Sol_{2.0}/Sol_{6.5}$ (µg/mL)[c]	h/m CL_{int} (µL/min/mg protein)[d]
1	a,a	4.5	41.1	<1.6/<1.6	10/7
2	l,l	3.0	66.9	12.5-25/12.5-25	<7/<7
3	h,h	1.3	66.9	>100/12.5-25	<7/188
4	k,k	0.8	92.7	6.3-12.5/6.3-12.5	18/157
5	n,n	4.4	78.1	<1.6/<1.6	<7/12
6	a,h	3.2	54.0	6.3-12.5/6.3-12.5	12/37
7	a,i	3.0	54.0	50-100/12.5-25	13/154
8	a,j	3.7	54.0	1.6-3.1/<1.6	188/705

9	a,k	3.0	66.9	1.6-3.1/<1.6	210/160
10	a,m	3.2	67.2	12.5-25/6.3-12.5	73/108
11	a,b	1.5	81.3	<1.6/12.5-25	<7/<7
12	a,f	1.6	81.3	1.6-3.1/12.5-25	<7/<7
13	a,c	2.7	84.2	6.3-12.5/6.3-12.5	28/22
14	a,g	3.3	84.2	1.6-3.1/1.6-3.1	81/69
15	a,d	3.8	64.9	<1.6/<1.6	<7/12
16	a,e	3.6	58.2	<1.6/<1.6	16/14
17	a,n	4.5	59.6	<1.6/<1.6	<7/<7
18	a,l	3.8	54.0	3.1-6.3/3.1-6.3	<7/<7
19	d,l	3.0	77.8	1.6-3.1/1.6-3.1	<7/<7
20	l,n	3.7	72.5	3.1-6.3/3.1-6.3	<7/16

[a]LogD values were estimated by correlation of their chromatographic retention properties using a modified gradient HPLC method adapted from Lombardo et al.[27]

[b]calculated using ChemAxon JChem for Excel

[c]Compounds in DMSO were spiked into either pH 6.5 phosphate buffer or 0.01 M HCl (approx. pH 2.0) and analyzed by nephelometry[28] to determine a concentration range.

[d]in vitro intrinsic clearance measured in human and mouse liver microsomes

Substitution of one of the 4-fluoro-3-trifluromethylphenyl substructures of **1** with azaheterocycles **6**-**10** decreased lipophilicity, and with the exception of **8** and **9**, increased solubility significantly. Replacing one of the 4-fluoro-3-trifluromethylphenyl substructures of **1** with benzoic acids (**11**, **12**), benzamides (**13**, **14**), a benzonitrile (**15**) or an acetophenone (**16**) decreased lipophilicity, and with the exception of **14**, **15**, and **16**, all were more soluble than **1**. Compounds where one of the 4-fluoro substituents were replaced with pyridine nitrogen atoms (**18** vs. **1**, **20** vs. **17**, **19** vs. **15**) were less lipophilic and marginally more soluble.

Twelve of twenty *N,N*-diaryl ureas (Table 1) had low intrinsic clearance values in human and mouse liver microsomes and three of these (**1**, **5**, **17**) were the most lipophilic of the series, possibly reflecting high protein binding in the microsomal test system. The eight *N,N*-diaryl ureas with intermediate to high intrinsic clearance contained either pyridine nitrogen atoms (**4**, **6**-**10**) or primary carboxamide functional groups (**13**, **14**). Notably, *N,N*-diaryl ureas with 3-trifluoromethyl-4-pyridyl substructures (**2**, **18**-**20**) were metabolically stable.

As a gatekeeping assessment of antischistosomal activity, the *N,N'*-diaryl ureas were tested against newly transformed schistosomula (NTS)[24] (Table 2). At 10 μM, 9 out of 20 of the compounds killed the NTS. A subsequent concentration titration revealed NTS IC_{50} values ranging from 0.15 to 5.6 μM. Further assessment indicated that these compounds killed adult *S. mansoni* at a similar IC_{50} range of 0.18 to 3.3 μM. The aryl substructures (Table 1) in the active *N,N'*-diaryl ureas were 4-fluoro-3-trifluoromethylphenyl = 3-trifluoromethyl-4-pyridyl > 2,2-difluorobenzodioxole > 4-benzonitrile. Notably, none of the new *N,N'*-diaryl ureas were more potent than **1** *ex vivo*.

Table 2. *Ex vivo* antischistosomal activity and cytotoxicity for selected *N,N'*-diarylureas.

	S. mansoni IC_{50} (μM)	Cytotoxicity IC_{50} (μM)

Compd	NTS	adult	HFF	U-20S	HEK293	HC-04
1	0.15	0.19	57	>100	>100	>100
2	2.4	0.88	>100	>100	>100	>100
5	0.26	0.49	79	>100	>100	>100
6	5.6	>10	ND	ND	ND	ND
15	1.6	0.94	60	>100	>100	>100
17	0.21	0.49	67	>100	>100	>100
18	0.74	0.66	71	>100	>100	>100
19	1.9	3.3	>100	>100	>100	>100
20	1.3	0.75	80	>100	>100	>100

To assess host cell cytotoxicity, the active *N,N′*-diaryl ureas were tested for growth inhibition of

four human cell lines: human foreskin fibroblast (HFF), kidney (HEK293), hepatocyte (HC04),

and B lymphocyte (RAJI) (Table 2). The HFF cell line was inhibited by 6 out of 8 of the

compounds with IC$_{50}$ values ranging from 57 to 80 μM; the remaining cell lines were unaffected

at compound concentrations up to 100 μM. Thus, these compounds appeared to have high

antischistosomal selectivity, although the six compounds that inhibited the HFF cell line were

also among the most potent against *ex vivo S. mansoni* with IC$_{50}$ values < 1 μM.

Single 100 mg/kg oral doses of the most active *N,N′*-diaryl ureas were administered to non-

infected mice to assess exposure (Table 3). For logistical reasons, we made the assumption that

exposure profiles generated in non-infected mice give a reasonable estimation of exposure in *S.*

mansoni-infected mice. Plasma concentrations of **1** increased until 2 h post-dose after which

they remained above 1 μM up to at least 48 h (Figure 2A). Similarly, plasma concentrations of **2**

and **18** increased until about 4 h post-dose and then remained high for the duration of the 48 h post-dose sampling period. Based on the AUC values up to the last measured concentration, the overall systemic exposures of **2** and **18** were approximately 2-4-fold higher than that of **1**. Absorption of **15** and **19** resulted in similar T_{max} and C_{max} values compared to **1**, **2**, and **18** (Table 1), however concentrations declined with a much shorter half-life than seen for either **1**, **2**, or **18** and were well below 1 μM by ~18 h post-dose. Based on *in vitro* studies with liver microsomes, both **15** and **19** were not highly susceptible to cytochrome P450-mediated metabolism, so alternative *in vivo* degradation/clearance pathways are likely for these benzonitriles. Unfortunately, the basis for these differences in half-life cannot be determined based only on the oral exposure data and additional studies with intravenous dosing would be needed to differentiate between absorption, distribution, and clearance-related differences.

Table 3. Exposure parameters and *in vivo* antischistosomal activity of selected *N,N′*-diarylureas following administration of a single 100 mg/kg oral dose.

Compd	C_{max} (μM)	T_{max} (h)	Half-Life (h)	$AUC_{0\text{-last}}$ (μM.h)	*S. mansoni* WBR (%)
1	31	4	11	394	40
2	40	4.0	10	953	20

5	25	c.n.d.	13	679	0
15	31	4	2.7	216	37
17	27	c.n.d.	c.n.d.	989	0
18	56	7.5	18	1486	50
19	20	2.0	2.3	175	1.6
20	55	c.n.d.	c.n.d.	2273	2.1

c.n.d. = could not determine

Following oral administration, **5**, **17**, and **20** were each very slowly absorbed and exhibited

relatively flat profiles precluding the assessment of T_{max} (Figure 2B). The shape of these profiles

likely reflects the high dose and very poor aqueous solubility leading to very prolonged

absorption. For these three 2,2-difluorobenzodioxole-containing *N,N*-diaryl ureas, plasma

concentrations remained above ~5 μM during the entire 48 h sampling period. Based on AUC_{0-last}

values ranging from 679 to 2273 μM.h, the exposure of **5**, **17**, and **20** was much higher than that

of **1** (394 μM.h) but comparable to that for **2** and **18** (953 and 1486 μM.h). From these data, we

see a trend that *N,N*-diaryl ureas containing 3-trifluoromethyl-4-pyridyl and 2,2-

difluorobenzodioxole substructures had the highest plasma exposures of the compounds tested.
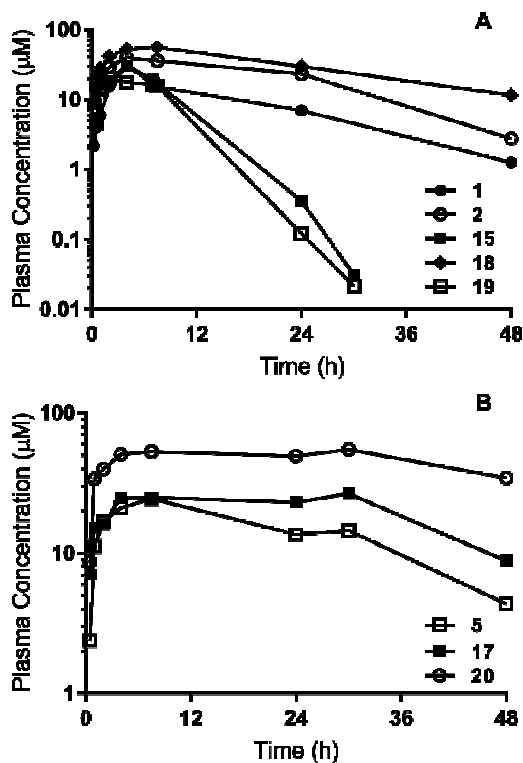
11

Figure 2. Plasma concentration versus time profiles following oral administration of 100 mg/kg to non-infected male Swiss outbred mice. Symbols represent the mean of n=2 mice at each time point. Panel A shows the profiles for **1**, **2**, **15**, **18**, and **19**. Panel B shows the profiles for **5**, **17**, and **20**.

In vivo antischistosomal activity was determined by measuring worm burden reduction (WBR) values following administration of single 100 mg/kg oral doses to *S. mansoni*-infected mice (Table 3). None of the compounds tested showed high *in vivo* activity, but the three (**1**, **15**, and **18**) with moderate WBR values (37-50%) contained a 4-fluoro-3-trifluoromethylphenyl substructure. We also found that at this same 100 mg/kg dose, MMV665852 had no activity (0% WBR). There was no direct correlation between plasma exposure and *in vivo* activity. For example, even though all compounds had C_{max} levels an order-of-magnitude greater than their *S.*

12

mansoni IC$_{50}$ values, and with the exception of **15** and **19**, maintained high plasma concentrations for extended periods, their overall *in vivo* efficacy was weak to moderate with only **1** and **18** having WBR values of 40-50%. When **18** was administered as four consecutive 80 mg/kg oral doses, the WBR of 53% was no better than that of 50% obtained with a single 100 mg/kg dose. Given that most of the compounds in this series are quite lipophilic (Log D >3), the disappointing *in vivo* efficacy despite high plasma exposure could be a reflection of high plasma protein binding and low unbound concentrations with insufficient concentrations reaching the site of action within the worms to achieve the desired killing effect. Additional pharmacokinetic and pharmacodynamic studies are needed to better understand the relationship between plasma and/or tissue exposure and *in vivo* activity for this series of compounds. Even though none of the *N,N*-diaryl ureas had high *in vivo* activity, it is useful to note that at this same 100 mg/kg dose, praziquantel also has a low WBR value of only 15%;[25] however, a higher 400 mg/kg dose of praziquantel reduces worm burden by 96%.[26]

In summary, replacement of one of the 4-fluoro-3-trifluoromethylphenyl substructures of **1** with azaheterocycles and benzoic acids, benzamides, or benzonitriles decreased lipophilicity, and in most cases, increased aqueous solubility. There was no clear relationship between lipophilicity and metabolic stability, although all *N,N*-diaryl ureas with 3-trifluoromethyl-4-pyridyl substructures were metabolically stable. *N,N'*-diaryl ureas containing 4-fluoro-3-trifluoromethylphenyl, 3-trifluoromethyl-4-pyridyl, 2,2-difluorobenzodioxole, or 4-benzonitrile substructures had high activity against *ex vivo S. mansoni* and relatively low cytotoxicity. *N,N*-diaryl ureas with 3-trifluoromethyl-4-pyridyl and 2,2-difluorobenzodioxole substructures had the highest exposures whereas those with 4-fluoro-3-trifluoromethylphenyl substructures had the

best *in vivo* antischistosomal activities. Finally, there was no direct correlation between compound exposure and *in vivo* activity.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at

References

1. Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J. Helminth infections: The great neglected tropical diseases. *J Clin Invest.* 2008;118:1311–1321.

2. Gryseels B. Schistosomiasis. *Infect Dis Clin North Am.* 2012;26:383–397.

3. Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. *Lancet* 2014; 383:2253–2264.

4. Vale N, Gouveia MJ, Rinaldi G, Brindley PJ, Gärtner F, Correia da Costa JM. Praziquantel for schistosomiasis: Single-drug metabolism revisited, mode of action, and resistance. *Antimicrob Agents Chemother.* 2017;61:e02582–16.

5. Melman SD, Steinauer ML, Cunningham C, Kubatko LS, Mwangi IN, Wynn NB, Mutuku, MW, Karanja DM, Colley DG, Black CL, Secor WE, Mkoji GM, Loker ES. Reduced susceptibility to praziquantel among naturally occurring Kenyan isolates of *Schistosoma mansoni*. *PLoS Negl Trop Dis.* 2009;3:e504.

6. Seto EY, Wong BK, Lu D, Zhong B. Human schistosomiasis resistance to praziquantel in China: Should we be worried? *Am J Trop Med Hyg.* 2011;85:74–82.

7. Kasinathan RS, Greenberg RM. Pharmacology and potential physiological significance of schistosome multidrug resistance transporters. *Exp Parasitol.* 2012;132:2–6.

8. Abdulla M-H, Ruelas DS, Wolff B, Snedecor J, Lim K-C, Xu F, Renslo AR, Williams J, McKerrow JH, Caffrey CR. Drug discovery for schistosomiasis: Hit and lead compounds identified in a library of known drugs by medium-throughput phenotypic screening *PLoS Negl Trop Dis* 2009;3:e478.

9. Ingram-Sieber K, Cowan N, Panic G, Vargas M, Mansour NR, Bickle QD, Wells TN, Spangenberg T, Keiser J. Orally active antischistosomal early leads identified from the open access malaria box. *PLoS Negl Trop Dis.* 2014;8:e2610.

10. Panic G,Vargas M, Keiser J, Scandale I. Activity profile of an FDA-approved compound library against *Schistosoma mansoni. PLoS Negl Trop Dis* 2015;9:e0003962.

11. Ferreira LG, Andricopulo AD. Drug repositioning approaches to parasitic diseases: A medicinal chemistry perspective. *Drug Discov Today* 2016;21:1699–1710.

12. Schebb NH, Inceoglu B, Ahn KC, Morisseau C, Gee SJ, Hammock BD. Investigation of human exposure to triclocarban after showering and preliminary evaluation of its biological effects. *Environ Sci Technol.* 2011;45:3109-3115.

13. Tonoli D, Fürstenberger C, Boccard J, Hochstrasser D, Jeanneret F, Odermatt A, Rudaz S. Steroidomic footprinting based on ultra-high performance liquid chromatography coupled with qualitative and quantitative high-resolution mass spectrometry for the evaluation of endocrine disrupting chemicals in H295R cells. *Chem Res Toxicol.* 2015;28:955–966.

14. Zhang Y, Anderson M, Weisman JL, Lu M, Choy CJ, Boyd VA, Price J, Sigal M, Clark J, Connelly M, Zhu F, Guiguemde WA, Jeffries C, Yang L, Lemoff A, Liou AP, Webb TR, Derisi

JL, Guy RK. Evaluation of diarylureas for activity against *Plasmodium falciparum*. *ACS Med Chem Lett* 2010;1:460–465.

15. Garuti L, Roberti M, Bottegoni G, Ferraro M. Diaryl urea: A privileged structure in anticancer agents. *Curr Med Chem.* 2016;23:1528–1548.

16. Siddique MUM, McCann GJ, Sonawane V, Horley N, Williams IS, Joshi P, Bharate SB, Jayaprakash V, Sinha BN, Chaudhuri B. Biphenyl urea derivatives as selective CYP1B1 inhibitors. *Org Biomol Chem.* 2016;14:8931–8936.

17. Cowan N, Dätwyler P, Ernst B, Wang C, Vennerstrom JL, Spangenberg T, Keiser, J. Activities of *N,N'*-Diarylurea MMV665852 analogs against *Schistosoma mansoni*. *Antimicrob Agents Chemother.* 2015;59:1935–1941.

18. Yao H, Liu F, Chen J, Li Y, Cui J, Qiao C. Antischistosomal activity of *N,N'*-arylurea analogs against *Schistosoma japonicum*. *Bioorg Med Chem Lett.* 2016;26:1386–1390.

19. Finger GC, Dickerson DR, Orlopp DE, Ehrmantraut JW. Aromatic fluorine compounds. XII. *N*-(fluorophenyl) carbamates. *J Med Chem.* 1964;7:572–573.

20. Wang C, Zhao Q, Vargas M, Jones JO, White KL, Shackleford DM, Chen G, Saunders J, Ng ACF, Chiu FCK, Dong Y, Charman SA, Keiser J, Vennerstrom JL. Revisiting the SAR of the antischistosomal aryl hydantoin (Ro 13-3978). *J Med Chem.* 2016;59:10705–10718.

21. Weilandt T, Troff RW, Saxell H, Rissanen K, Schalley CA. Metallo-supramolecular self-assembly: the case of triangle-square equilibria. *Inorg Chem.* 2008;47:7588–7598.

22. Stanovnik B, Tisler M, Golob V, Hvala I, Nikolic O. Heterocycles. CXCVIII. Heteroacyl azides as acylating agents for aromatic or heteroaromatic amines. *J Heterocyclic Chem.* 1980; 17:733–736.

23. Palm K, Stenberg P, Luthman K, Artursson P. Polar molecular surface properties predict the intestinal absorption of drugs in humans. *Pharm Res.* 1997;14:568–571.

24. Keiser J. In vitro and in vivo trematode models for chemotherapeutic studies. *Parasitology* 2010;137:589–603.

25. Keiser J, Manneck T, Vargas M. Interactions of mefloquine with praziquantel in the *Schistosoma mansoni* mouse model and in vitro. *J Antimicrob Chemother.* 2011;66:1791–1797.

26. Dong Y, Chollet J, Vargas M, Mansour NR, Bickle Q, Alnouti Y, Huang J, Keiser J, Vennerstrom JL. Praziquantel analogs with activity against juvenile *Schistosoma mansoni*. *Bioorg Med Chem Lett.* 2010;20:2481–2484.

27. Lombardo F, Shalaeva MY, Tupper KA, Gao F. ElogD$_{oct}$: A tool for lipophilicity determination in drug discovery. 2. basic and neutral compounds. *J Med Chem.* 2001;44:2490–2497.

28. Bevan CD, Lloyd RS. A high-throughput screening method for the determination of aqueous drug solubility using laser nephelometry in microtiter plates. *Anal Chem.* 2000;72:1781–1787

Highlights

► Expansion of antischistosomal *N,N'*-diaryl urea SAR.

► 3-Trifluoromethyl-4-pyridyl and 2,2-difluorobenzodioxole improve exposure.

► 4-Fluoro-3-trifluoromethylphenyl required for best antischistosomal activity.