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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], and **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

Abstract

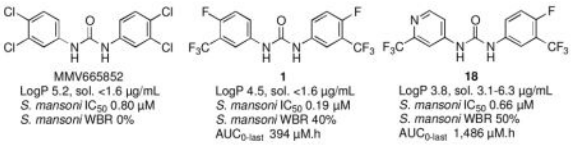
N,N′-diarylureas have recently emerged as a new antischistosomal chemotype. We now describe physicochemical profiling, *in vitro* ADME, plasma exposure, and *ex vivo* and *in vivo* activities against *Schistosoma mansoni* for twenty new *N,N′*-diarylureas designed primarily to increase aqueous solubility, 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.

Graphical Abstract

tel: 402.559.5362, fax: 402.559.9543, jvenners@unmc.edu.

A. Supplementary data

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



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).

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 M 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 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).

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.

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*.

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.

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 $AUC_{0\text{-last}}$ 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.

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. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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.

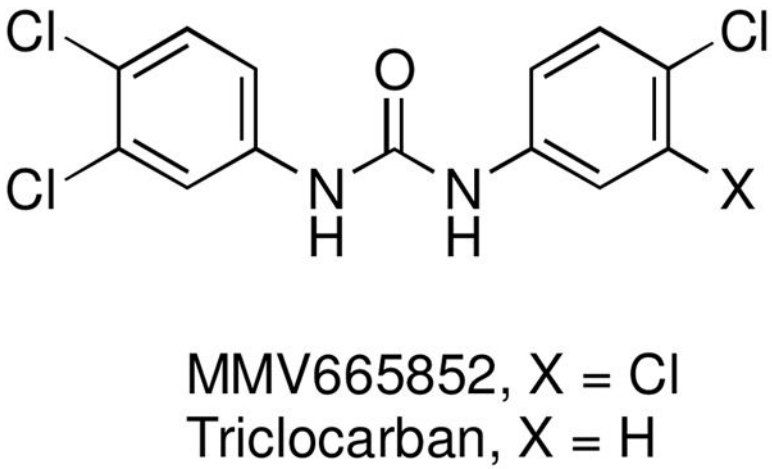


Figure 1.

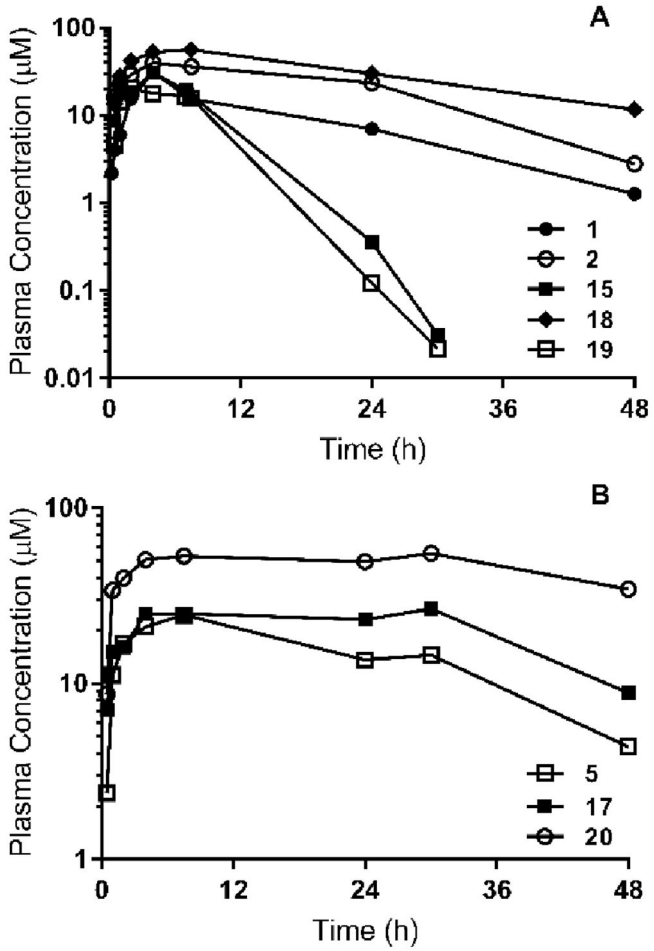
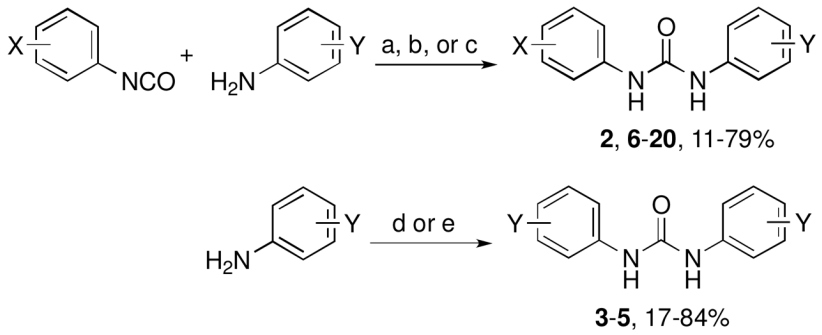


Figure 2.

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**.



Scheme 1.

Reagents and conditions: (a) *N,N*-diisopropylethylamine, CH_2Cl_2, rt, 12 h (**2**, **17**, **18**); (b) THF, 25–80 °C; 12 h (**6–9**, **19**, **20**); (c) CH_3CN, 80 °C, 12 h (**10–16**); (d) CDI, THF, rt, 48 h (**3**, **4**); (e) CDI, 1,2-dimethoxyethane, reflux, 16 h (**5**).

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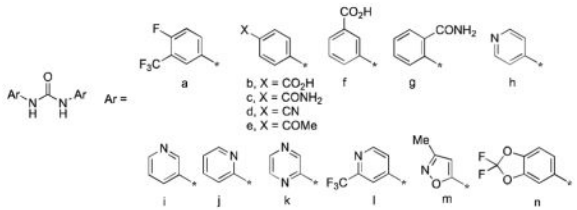
Table 1

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

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

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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