ACS Infectious Diseases

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Antiprotozoal Selectivity of Diimidazoline *N*-Phenylbenzamides

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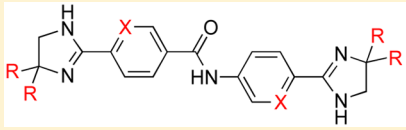
Supporting Information

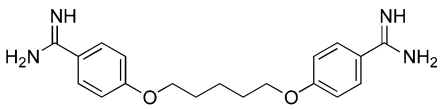


X, R	CH, H	N, H	CH, CH_3
P. falciparum IC_{50}	1.9 nM	28 nM	310 nM
T. b rhodesiense IC_{50}	86 nM	8,300 nM	26 nM
cytotoxicity IC_{50}	68,000 nM	130,000 nM	>150,000 nM

ABSTRACT: We discovered three diimidazolines with high antiplasmodial selectivity that had IC_{50} values of 1.9−28 nM against cultured *Plasmodium falciparum*. We also identified a *gem*-dimethyl diimidazoline with high antitrypanosomal selectivity that had an IC_{50} value of 26 nM against cultured *Trypanosoma brucei rhodesiense*. Two 2-imidazoline heterocycles in a para orientation on a *N*-phenylbenzamide or similar core structure were required for high antiprotozoal activity. Ring expansion of the imidazoline as well as heterocyclic variants with pK_a values of <7 all decreased activity significantly.

KEYWORDS: *diamidine, diimidazoline, antimalarial, antiprotozoal, antitrypanosomal, N-phenylbenzamide*

Diamidines, diimidazolines, and their structural analogues are well-known for their high activity against human African trypanosomiasis (HAT), also known as sleeping sickness. Many of these same compounds also have high activities against malaria, another vector-borne protozoal disease.[1,2] Pentamidine (**1**) (Figure 1) is the only clinically approved diamidine, although much effort has been directed to identifying an orally active next-generation drug with a better therapeutic index. As reviewed by Werbovetz,[2] diamidines seem to inhibit the growth of HAT and malaria species by different mechanisms. For HAT, diamidines selectively accumulate in the parasite by way of the P2 nucleoside transporter and subsequently concentrate in the mitochondrion, where they bind to kinetoplast DNA. For malaria, diamidines selectively concentrate in infected red blood cells, possibly by a choline transporter and by binding to hematin, where they then inhibit hemozoin formation.



Pentamidine (**1**)

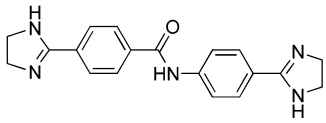


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Figure 1. Structures of pentamidine (**1**) and diimidazoline **2**.

Our initial interest in diimidazolines arose from their potential as inhibitors of botulinum neurotoxin.[3] Recently, we identified several diimidazoline mono- and diamides that were as potent as pentamidine against HAT, but were less cytotoxic.[4] As a follow-up to this investigation, we discovered that diimidazoline *N*-phenylbenzamide **2** also had potent antimalarial activity with an IC_{50} value of 1.9 nM against the NF54 strain of *Plasmodium falciparum*. The molecular weight, aromatic ring count,[5] and calculated[6] Log *P* value of 1.9 ± 1.0 for **2** suggest that this prototype is an attractive medicinal chemistry starting point. Thus, we set out to further investigate the antiprotozoal activity of **2** and begin to define its structure−activity relationship (SAR) by the synthesis of **3**−**24**.

RESULTS AND DISCUSSION

As shown in Scheme 1, diimidazolines **3**, **5**, **10**, and **11** and monoimidazolines **23** and **24** were obtained by treatment of the commercially available or known[7−9] dinitrile or nitrile precursors **25**−**30** with ethylenediamine and sodium hydrosulfide[10] in dimethylacetamide (DMA). The first four of these were isolated as their mesylate (**3**) or dimesylate (**5**, **10**, **11**) salts by treatment with methanesulfonic acid (MSA) (31−81% overall reaction yields).

As shown in Scheme 2, carboxyphthalimide **31**[11] was amidated to form 4-cyanoanilide **32**, deprotected with hydrazine to form **33**, and then transformed[10] into amino imidazoline **9** as described above. Diimidazole **12** was obtained by high-temperature Pd-catalyzed dehydrogenation[12] of **2**.

Received: December 6, 2014
Published: January 14, 2015

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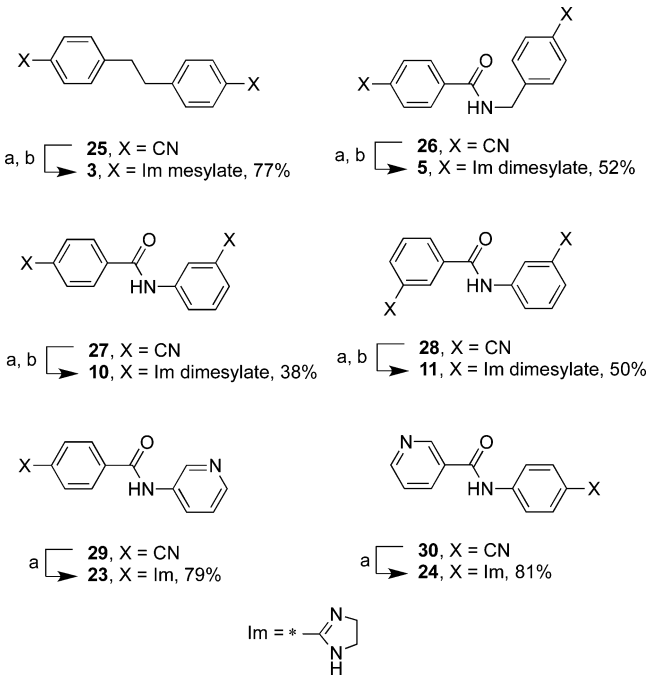
DOI: 10.1021/id500034v
ACS Infect. Dis. 2015, 1, 135−139

Scheme 1[a]



[a]Reagents and conditions: (a) ethylenediamine, NaSH, DMA, 120 °C, 2 h; (b) MSA, CH_3CN, 50−70 °C, 0.5 h.

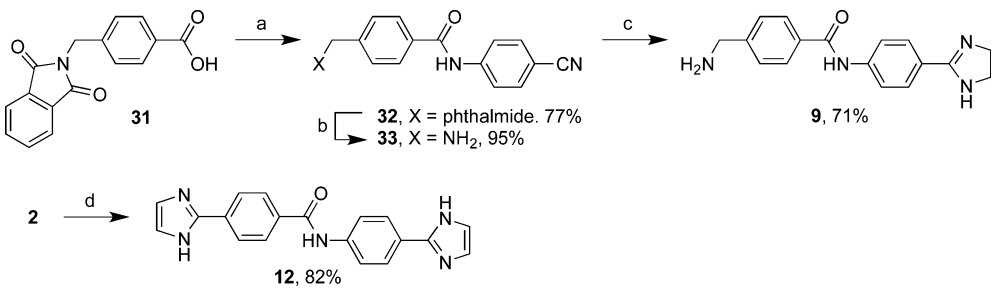
As shown in Scheme 3, thiazoline **13** and oxazoline **14** were obtained in low to moderate yields from the common dintrile precursor **34** by reaction with cysteamine hydrochloride or 2-amino-2-methyl-1-propanol with a $ZnCl_2$ catalyst[13] in hot DMA. Diimidazolines **15** and **16** and tetrahydropyridines **17** and **18** were obtained from a mixture of **34** and the corresponding diamines with sodium hydrosulfide[10] in hot DMA in 37−60% yields. Compounds **16** and **18** were isolated as their dimesylate and mesylate salts by treatment with MSA. Dibenzylamine **19** was obtained by hydrogenation of **34** with a Raney Ni catalyst.[14]

The synthesis of diimidazolines **20**−**22** began with the synthesis of their dinitrile amide precursors **39**−**41** from combinations of acid chloride **35**, acid **36**, and 4-aminobenzonitriles **37** and **38** in 50−67% yields (Scheme 4). Nitrile to imidazoline followed by formation of the dimesylate salts proceeded as already described to afford **20**−**22**. Known diimidazolines **2**,[4] **4**,[15] **6**,[16] **7**,[17] and **8**[17] (Table 1) were obtained by reaction sequences similar to those described in Schemes 1−3.

In vitro antiprotozoal activity (Tables 1−3) was measured using the chloroquine-sensitive NF54 strain of *P. falciparum*[18] and the STIB900 strain of *T. brucei rhodesiense*.[19] As previously described,[19] in vitro cytotoxicity was assessed using the rat myoblast L6 cell line. Replacing the central carboxamide of **2** with ethylene (**3**) or ether (**4**) substructures reduced activity against both protozoa by an order of magnitude (Table 1). In **5**, activity was reduced still further by insertion of a methylene carbon α to the NH of the carboxamide; in contrast, potency was restored in **6**, the isosteric urea. This suggests that the aniline nitrogen para to a 2-imidazoline substituent in both **2** and **5** is a key structural element associated with high antiprotozoal activity. Yet, this same substructure is present in imidazoline **7** and aminomethyl imidazoline **9**, but the data from these and imidazoline **8** clearly show that two imidazolines are required for high activity. Furthermore, the weak activity of meta regioisomers **10** and **11** shows that two imidazolines in a para orientation are required for optimal activity. For the compounds depicted in Table 1, there was no clear correlation between antiprotozoal activity and cytotoxicity.

The SAR of the 2-imidazoline substructure of **2** is shown in Table 2. Diimidazole **12**, dithiazoline **13**, and dioxazoline **14** show that decreasing the basicity of the imidazoline in **2** from the estimated pK_a value of 10[15,20,21] to 4−7[20,22] reduced activity against both protozoa by 2−4 orders of magnitude. Similarly, it was demonstrated[23] that the tetrazole (acidic) analogue of **1** had no activity against *T. b. rhodesiense* and was 2 orders of magnitude less potent than **1** (pK_a = 11.4)[24] against *P. falciparum*. However, for **15**−**19**, the SARs for the two protozoans diverged. Against *P. falciparum*, both alkyl substitution (**15**, **16**) and ring expansion (**17**, **18**) of the imidazoline decreased activity significantly as did replacement of the imidazoline with a benzylamine (**19**). Compounds **15**−**19**, with estimated pK_a values in the range of 9−12,[20] show that two weak base functional groups are insufficient for high antiplasmodial activity and demonstrate the unique contribution of the two imidazoline heterocycles in **2** to its high activity. On the other hand, against *T. b. rhodesiense*, we found that **15**, with its *gem*-dimethyl imidazolines, was 3-fold more potent than **2** and had high antitrypanosomal selectivity. Similarly, the ring-fused imidazoline **16** had modest HAT selectivity, although it was 2-fold less potent than **2**. Lastly, **17**−**19** were 1−2 orders of magnitude less potent than **2**.

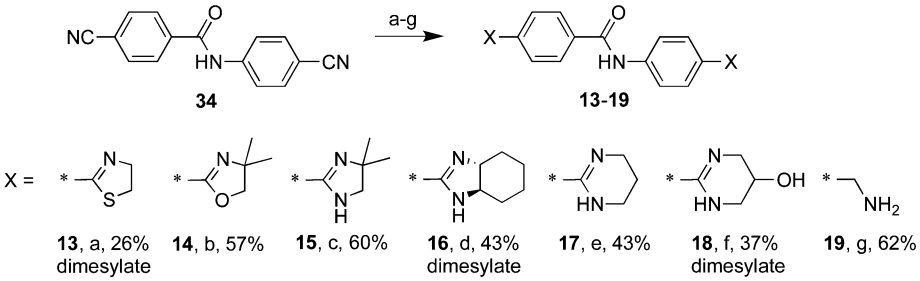
Scheme 2[a]



[a]Reagents and conditions: (a) $SOCl_2$, DMF, CH_2Cl_2 then 4-aminobenzonitrile, TEA, CH_2Cl_2, room temperature, 24 h; (b) hydrazine hydrate, $MeOH/CHCl_3$ 1:7, 50 °C, 24 h; (c) ethylenediamine, NaSH, DMA, 120 °C, 2 h; (d) 5% Pd/C, 120 °C, 20 h.

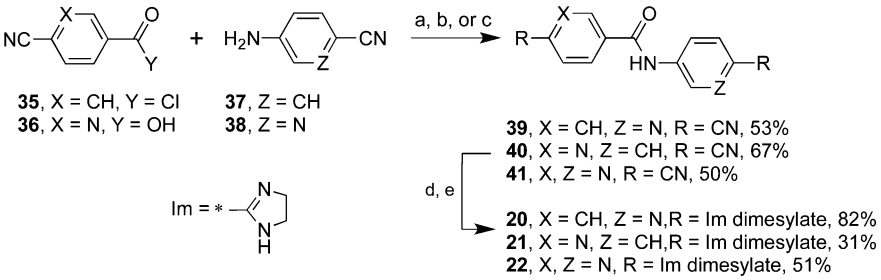
DOI: 10.1021/id500034v
ACS Infect. Dis. 2015, 1, 135−139

Scheme 3[a]



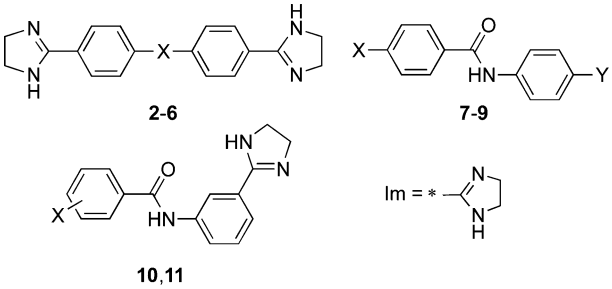
[a]Reagents and conditions: (a) cysteamine hydrochloride, $ZnCl_2$, DMA, 120 °C, 24 h; (b) 2-amino-2-methyl-1-propanol, $ZnCl_2$, DMA, 130 °C, 24 h; (c) 2-methyl-1,2-propanediamine, NaSH, DMA, 100 °C, 2 h; (d) (±)-*trans*-1,2-diaminocyclohexane, NaSH, DMA, 120 °C, 20 h, then MsOH, CH_3CN, 50 °C, 0.5 h; (e) 1,3-propanediamine, NaSH, DMA, 100 °C, 2 h; (f) 1,3-diamino-2-propanol, NaSH, DMA, 120 °C, 20 h, then MSA, CH_3CN, 50 °C, 0.5 h; (g) H_2 60 psi, Raney Ni, NH_4OH/EtOH 1:20, 60 °C, 20 h.

Scheme 4[a]



[a]Reagents and conditions: (a) TEA, DMA, 0−25 °C, 24 h; (b) $SOCl_2$, DMF in CH_2Cl_2, room temperature, 24 h, then TEA, DMA, room temperature, 24 h; (c) HOBt, EDCl, TEA, DMA, room temperature, 24 h; (d) ethylenediamine, NaSH, DMA, 120 °C, 2 h; (e) MSA, CH_3CN, 50 °C, 0.5 h.

Table 1. In Vitro Antiprotozoal Activity of 2−11 against *P. falciparum* and *T. brucei rhodesiense* and in Vitro Cytotoxicity against the L6 Cell Line

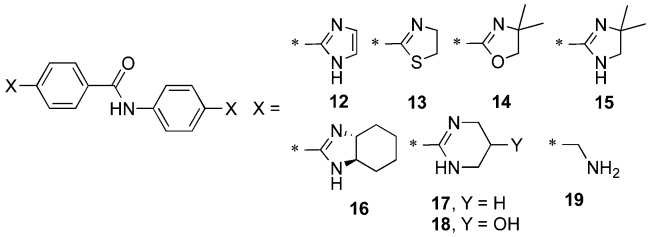


compd	X	Y	IC$_{50}$ (nM) *P. falciparum*[a]	*T. b. rhodesiense*[b]	L6
2[c]	CONH		1.9	86	68000
3[d]	CH_2CH_2		22	2300	11000
4[d]	O		97	590	55000
5[c]	$CONHCH_2$		5700	91000	>150000
6	NHCONH		5.7	60	23000
7	H	Im	11000	49000	130000
8[d]	Im	H	8900	13000	>150000
9	CH_2NH_2	Im	1000	2100	40000
10[c]	4-Im		800	760	>150000
11[c]	3-Im		700	1200	140000
chloroquine			5.8	>100000	>100000
pentamidine[e](**1**)			56	1.5	5100

[a]NF54 strain. [b]STIB900 strain. [c]Isolated and tested as the dimesylate salt. [d]Isolated and tested as the mesylate salt. [e]Data from Dong et al.[4] and Athri et al.[29]

DOI: 10.1021/id500034v
ACS Infect. Dis. 2015, 1, 135−139

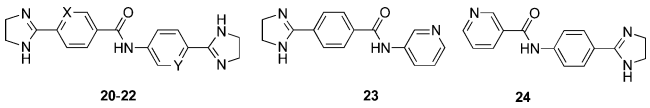
Table 2. In Vitro Antiprotozoal Activity of 12−19 against *P. falciparum* and *T. brucei rhodesiense* and in Vitro Cytotoxicity against the L6 Cell Line



compd	IC$_{50}$ (nM)		
	P. falciparum	*T. b. rhodesiense*	L6
12	1300	120000	40000
13[a]	4800	2200	34000
14	130000	>150000	>150000
15	310	26	>150000
16[a]	650	210	55000
17	470	950	>150000
18[b]	7900	8700	>150000
19[a]	7200	920	>150000

[a]Isolated and tested as the dimesylate salt. [b]Isolated and tested as the mesylate salt.

Table 3. In Vitro Antiprotozoal Activity of 20−24 against *P. falciparum* and *T. brucei rhodesiense* and in Vitro Cytotoxicity against the L6 Cell Line



compd	X	Y	IC$_{50}$ (nM)		
			P. falciparum	*T. b. rhodesiense*	L6
20[a]	CH	N	21	140	110000
21[a]	N	CH	23	240	>150000
22[a]	N	N	28	8300	130000
23			36000	>150000	>150000
24			98000	>150000	>150000

[a]Isolated and tested as the dimesylate salt.

Data for **20**−**22**, the three 2-pyridyl isosteres of **2**, and their monoimidazoline controls **23** and **24** are shown in Table 3. The electronegative pyridine nitrogen atoms in **20**−**22** are predicted to decrease the pK_a values of the adjacent imidazoline heterocycles by ≥1 pK_a unit.[20] Compared to **2**, we note that **20** and **21** were only slightly less potent and **22** was 148-fold less potent against *T. b. rhodesiense* but that all three 2-pyridyl isosteres were only 11−15-fold less potent against *P. falciparum*. In contrast to these SAR trends, Bakunova et al.[19] found that the 2-pyridyl analogue of pentamidine was 3- and 6-fold more potent than parent drug against *T. b. rhodesiense* and *P. falciparum*, respectively. Interestingly, a monopyridyl benzamide with an IC$_{50}$ of 45 nM against *T. b. rhodesiense* was recently discovered.[25] Finally, as we had previously observed for **7** and **8** (Table 1), monoimidazolines **23** and **24** had very weak activities despite their pyridyl nitrogen atoms.

To summarize, we identified three diimidazolines (**2**, **6**, and **22**) with high antiplasmodial selectivity; of these, *N*-phenylbenzamide **2** and *N*,*N*′-diphenylurea **5** were as potent as chloroquine against cultured *P. falciparum*. We also identified *N*-phenylbenzamide **15**, with its *gem*-dimethyl imidazolines, as a new compound with high antitrypanosomal selectivity. We found that two 2-imidazoline heterocycles in a para orientation on a *N*-phenylbenzamide or similar core structure were required for high antiprotozoal activity. Ring expansion of the imidazoline as well as heterocyclic variants with pK_a values <7 all decreased activity significantly. Future work will further define the SAR of this compound series with a goal to increase antiprotozoal efficacy and selectivity.[26−28]

METHODS

Target Compound Characterization. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a 500 MHz spectrometer. All chemical shifts are reported in parts per million (ppm) and are relative to internal $(CH_3)_4Si$ (0 ppm) for ^{1}H or DMSO-d_6 (39.7 ppm) for ^{13}C NMR. Combustion and HPLC analysis confirmed that all target compounds possessed purities ≥95%. As indicated in the Supporting Information, starting materials were commercially available or were prepared according to known procedures.

In Vitro Activity Assays. As previously described,[4,18] in vitro antiprotozoal activities were measured using the chloroquine-sensitive NF54 strain of *P. falciparum* and the STIB900 strain of *T. brucei rhodesiense*.

ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/id500034v.

Synthesis and characterization of **3**, **5**, and **9**−**24** (PDF)

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Author Contributions

X.W., Y.D., M.C., M.K., and S.W. generated and analyzed data. X.W., Y.D., and J.L.V. analyzed data and wrote the paper.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This investigation received financial support from Medicines for Malaria Venture and the Swiss Tropical and Public Health Institute. We thank Mark Gardner and Paul Willis of Medicines for Malaria Venture for their advice and support.

ABBREVIATIONS

DMA, dimethylacetamide; HAT, human African trypanosomiasis; Im, imidazoline; MSA, methanesulfonic acid

REFERENCES

(1) Soeiro, M. N. C., De Souza, E. M., Stephens, C. E., and Boykin, D. W. (2005) Aromatic diamidines as antiparasitic agents. *Expert Opin. Invest. Drugs 14*, 957−972.

(2) Werbovetz, K. (2006) Diamidines as antitrypanosomal, antileishmanial, and antimalarial agents. *Curr. Opin. Invest. Drugs 7*, 147−157.

(3) Nuss, J. E., Dong, Y., Wanner, L. M., Ruthel, G., Wipf, P., Gussio, R., Vennerstrom, J. L., Bavari, S., and Burnett, J. C. (2010) Pharmacophore refinement guides the design of nanomolar-range Botulinum neurotoxin serotype A light chain inhibitors. *ACS Med. Chem. Lett. 1*, 301−305.

DOI: 10.1021/id500034v
ACS Infect. Dis. 2015, 1, 135−139

(4) Dong, Y., Wang, X., Cal, M., Kaiser, M., and Vennerstrom, J. L. (2014) Activity of diimidazoline amides against African trypanosomiasis. *Bioorg. Med. Chem. Lett. 24*, 944−948.

(5) Ritchie, T. J., and MacDonald, S. J. F. (2009) The impact of aromatic ring count on compound developability: Are too many aromatic rings a liability in drug design? *Drug Discovery Today 14*, 1011−1020.

(6) Tetko, I. V., Gasteiger, J., Todeschini, R., Mauri, A., Livingstone, D., Ertl, P., Palyulin, V. A., Radchenko, E. V., Zefirov, N. S., Makarenko, A. S., Tanchuk, V. Y., and Prokopenko, V. V. (2005) Virtual computational chemistry laboratory − design and description. *J. Comput. Aid. Mol. Des. 19*, 453−463.

(7) Makovec, F., Peris, W., Revel, L., Giovanetti, R., Redaelli, D., and Rovati, L. C. (1992) Antiallergic and cytoprotective activity of new *N*-phenylbenzamido acid derivatives. *J. Med. Chem. 35*, 3633−3640.

(8) Romero, M., Harrak, Y., Basset, J., Orue, J. A., and Pujol, M. D. (2009) Direct synthesis of primary arylamines via C-N cross-coupling of aryl bromides and triflates with amides. *Tetrahedron 65*, 1951−1956.

(9) Zimmer, C., Hafner, M., Zender, M., Ammann, D., Hartmann, R. W., and Vock, C. A. (2011) *N*-(Pyridin-3-yl)benzamides as selective inhibitors of human aldosterone synthase (CYP11B2). *Bioorg. Med. Chem. Lett. 21*, 186−190.

(10) Sun, M., Wei, H.-T., Li, D., Zheng, Y.-G., Cai, J., and Ji, M. (2008) Mild and efficient one-pot synthesis of 2-imidazolines from nitriles using sodium hydrosulfide as catalyst. *Synth. Commun. 38*, 3151−3158.

(11) Vaisburg, A., Paquin, I., Bernstein, N., Frechette, S., Gaudette, F., Leit, S., Moradei, O., Raeppel, S., Zhou, N., Bouchain, G., Woo, S. H., Jin, Z., Gillespie, J., Wang, J., Fournel, M., Yan, P. T., Trachy-Bourget, M.-C., Robert, M.-F., Lu, A., Yuk, J., Rahil, J., MacLeod, A. R., Besterman, J. M., Li, Z., and Delorme, D. (2007) *N*-(2-Aminophenyl)-4-(heteroarylmethyl)-benzamides as new histone deacetylase inhibitors. *Bioorg. Med. Chem. Lett. 17*, 6729−6733.

(12) Pařík, P., Šenauerová, S., Lišková, V., Handlíř, K., and Ludwig, M. (2006) Study of synthesis of 2-(2-alkoxyphenyl)-1*H*-imidazoles. Comparison of oxidative aromatization reactions of imidazolines. *J. Heterocycl. Chem. 43*, 835−841.

(13) Minkkilä, A., Myllymäki, M. J., Saario, S. M., Castillo-Melendez, J. A., Koskinen, A. M. P., Fowler, C. J., Leppänen, J., and Nevalainen, T. (2009) The synthesis and biological evaluation of para-substituted phenolic *N*-alkyl carbamates as endocannabinoid hydrolyzing enzyme inhibitors. *Eur. J. Med. Chem. 44*, 2994−3008.

(14) Gillespie, R. J., Bamford, S. J., Botting, R., Comer, M., Denny, S., Gaur, S., Griffin, M., Jordan, A. M., Knight, A. R., Lerpiniere, J., Leonardi, S., Lightowler, S., McAteer, S., Merrett, A., Misra, A., Padfield, A., Reece, M., Saadi, M., Selwood, D. L., Stratton, G. C., Surry, D., Todd, R., Tong, X., Ruston, V., Upton, R., and Weiss, S. M. (2009) Antagonists of the human A2A adenosine receptor. 4. Design, synthesis, and preclinical evaluation of 7-aryltriazolo[4,5-*d*]-pyrimidines. *J. Med. Chem. 32*, 33−47.

(15) Crane, L., Anastassiadou, M., El Hage, S., Stigliani, J. L., Baziard-Mouysset, G., Payard, M., Leger, J. M., Bizot-Espiard, J.-G., Ktorza, A., Caignard, D.-H., and Renard, P. (2006) Design and synthesis of novel imidazoline derivatives with potent antihyperglycemic activity in a rat model of type 2 diabetes. *Bioorg. Med. Chem. 14*, 7419−7433.

(16) Schmidt, G., Hirt, R., and Fischer, R. (1969) Babesicidal effect of basically substituted carbanilides. I. Activity against *Babesia rodhaini* in mice. *Res. Vet. Sci. 10*, 530−533.

(17) Paal, M., Ruehter, G., Schotten, T. (2000) Preparation of imidazoline derivatives for the treatment of diabetes, especially type II diabetes. PCT Int. Appl. WO 2000078726 A1 20001228.

(18) Vennerstrom, J. L., Arbe-Barnes, S., Brun, R., Charman, S. A., Chiu, F. C. K., Chollet, J., Dong, Y., Dorn, A., Hunziker, D., Matile, H., McIntosh, K., Padmanilayam, M., Santo Tomas, J., Scheurer, C., Scorneaux, B., Tang, Y., Urwyler, H., Wittlin, S., and Charman, W. N. (2004) Identification of an antimalarial synthetic trioxolane drug development candidate. *Nature 430*, 900−904.

(19) Bakunova, S. M., Bakunov, S. A., Wenzler, T., Barszcz, T., Werbovetz, K. A., Brun, R., and Tidwell, R. R. (2009) Synthesis and antiprotozoal activity of pyridyl analogues of pentamidine. *J. Med. Chem. 52*, 4657−4667.

(20) Calculated pK_a values using ACD V11.02 software as implemented in SciFinder Scholar.

(21) As described in this reference and reference 15, 2-imidazolines have an experimentally observed pK_a range of 8.6−10.4 Remko, M., Swart, M., and Bickelhaupt, F. M. (2006) Theoretical study of structure, pK_a, lipophilicity, solubility, absorption, and polar surface area of some centrally acting antihypertensives. *Bioorg. Med. Chem. 14*, 1715−1728.

(22) Johansen, M., and Bundgaard, H. (1983) Prodrugs as drug delivery systems XXV: hydrolysis of oxazolidines − a potential new prodrug type. *J. Pharm. Sci. 72*, 1294−1298.

(23) Bakunova, S. M., Bakunov, S. A., Patrick, D. A., Kumar, E. V., Ohemeng, K. A., Bridges, A. S., Wenzler, T., Barszcz, T., Jones, S. K., Werbovetz, K. A., Brun, R., and Tidwell, R. R. (2009) Structure-activity study of pentamidine analogues as antiprotozoal agents. *J. Med. Chem. 52*, 2016−2035.

(24) Prankerd, R. J. (2007) Critical compilation of pK_a values for pharmaceutical substances. In *Profiles of Drug Substances, Excipients, and Related Methodology*, Vol. 33 (Brattain, H. G., Ed.), Elsevier, Amsterdam, The Netherlands.

(25) Ferrins, L., Gazdik, M., Rahmani, R., Varghese, S., Sykes, M. L., Jones, A. J., Avery, V. M., White, K. L., Ryan, E., Charman, S. A., Kaiser, M., Bergström, C. A., and Baell, J. B. (2014) Pyridyl benzamides as a novel class of potent inhibitors for the kinetoplastid *Trypanosoma brucei*. *J. Med. Chem. 57*, 6393−6402.

(26) Peters, J.-U., Schnider, P., Mattei, P., and Kansy, M. (2009) Pharmacological promiscuity: dependence on compound properties and target specificity in a set of recent Roche compounds. *ChemMedChem. 4*, 680−686.

(27) Edwards, M. P., and Price, D. A. (2010) Role of physicochemical properties and ligand lipophilicity efficiency in addressing drug safety risks. *Annu. Rep. Med. Chem. 45*, 381−391.

(28) Huang, T. L., Mayence, A., and Vanden Eynde, J. J. (2014) Some non-conventional biomolecular targets for diamidines. A short survey. *Bioorg. Med. Chem. 22*, 1983−1992.

(29) Athri, P., Wenzler, T., Tidwell, R., Bakunova, S. M., and Wilson, W. D. (2010) Pharmacophore model for pentamidine analogs active against *Plasmodium falciparum*. *Eur. J. Med. Chem. 45*, 6147−6151.

DOI: 10.1021/id500034v
ACS Infect. Dis. 2015, 1, 135−139