ACS Medicinal Chemistry Letters

Letter

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ACS Med. Chem. Lett., **Just Accepted Manuscript** • DOI: 10.1021/acsmedchemlett.7b00011 • Publication Date (Web): 05 Feb 2017

ACS Publications

ACS Medicinal Chemistry Letters is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Antiparasitic Lead Discovery: Towards Optimization of a Chemotype with Activity Against Multiple Protozoan Parasites

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KEYWORDS: *Antiparasitic agents;* Trypanosoma brucei; Trypanosoma cruzi; Leishmania major; Plasmodium falciparum*; Chagas disease, leishmaniasis; human African trypanosomiasis.*

ABSTRACT: Human African trypanosomiasis (HAT), Chagas disease, and leishmaniasis present a significant burden across the developing world. Existing therapeutics for these protozoal neglected tropical diseases suffer from severe side effects and toxicity. Previously, NEU-1045 (**3**) was identified as a promising lead with cross-pathogen activity, though it possessed poor physicochemical properties. We have designed a library of analogs with improved calculated physicochemical properties built on the quinoline scaffold of **3** incorporating small, polar aminoheterocycles in place of the 4-(3-fluorobenzyloxy)aniline substituent. We report the biological activity of these inhibitors against *Trypanosoma brucei* (HAT), *T. cruzi* (Chagas disease), and *Leishmania major* (cutaneous leishmaniasis), and describe the identification of N-(5-chloropyrimidin-2-yl)-6-(4-(morpholinosulfonyl)phenyl)quinolin-4-amine (**13t**) as a promising inhibitor of *L. major* proliferation and 6-(4-(morpholinosulfonyl)phenyl)-N-(pyrimidin-4-yl)quinolin-4-amine (**13j**), a potent inhibitor of *T. brucei* proliferation with improved drug-like properties.

Taken together, human African trypanosomiasis (HAT), Chagas disease, and leishmaniasis are responsible for 4.4 million disability adjusted life years (DALY) and 70,000 deaths annually.[1] Caused by the protozoan parasites *Trypanosoma brucei*, *T. cruzi*, and *Leishmania* spp., respectively, these diseases are spread through insect vectors across Latin America, Africa, and parts of southern Asia.[2-6] Current therapeutics suffer from severe side effects, complex and prolonged dosing regimens, high costs, and emerging resistance necessitating the need for new treatments.[7-12]

Our group has reported the discovery of the anti-trypanosomal activity of a library of compounds derived from a known tyrosine kinase inhibitor, lapatinib (**1**, **Figure 1**).[13-16] Owing to the high degree of homology in kinetoplastid protein kinases (PKs) in *T. brucei*, *T. cruzi*, and *L. major*,[17] we expected these compounds to be active against other trypanosomatid parasites. Thus, we tested new compounds against cultures of *T. brucei*, *T. cruzi*, and *L. major*. We also included *Plasmodium falciparum,* the causative agent of malaria, in this work. We identified two promising compounds as new leads for leishmaniasis - **NEU-554** (**2**) and **NEU-1045** (**3**, **Figure 1**) - which were evolved from the highly potent inhibitor of *T. brucei* growth, **NEU-617** (**4**).[14] Physicochemical analysis of this collection of compounds revealed they generally showed poor drug-like properties (**Figure 1** and **Table 1**), and subsequent efforts have been focused on the development of new of analogs aimed at improving these properties and overall lead quality (as described by lipophilic ligand effieicncy (LLE))[18] while maintaining, or improving *in vitro* activity against the parasites. Consistent with our practice, we tested compounds against multiple kinetoplastid parasites in parallel. The results of these efforts are reported herein.

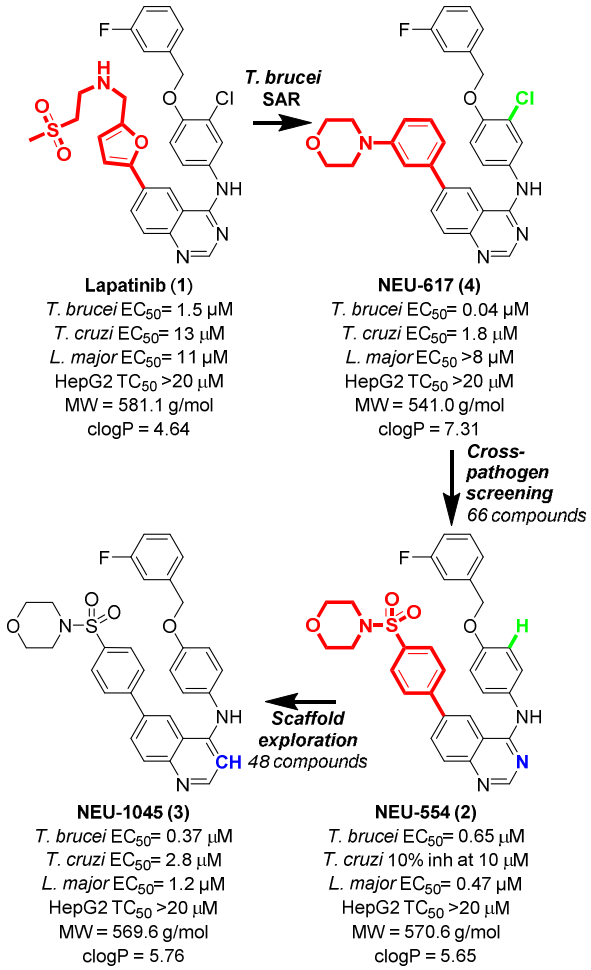
Table 1. Druglike properties of 3.

	3	**Goal**
Molecular weight	569.6	≤500
clogP	5.76	≤5
Protein binding (% free)	<0.03	>10
Aqueous solubility (μM)	2	>50
Human liver microsomes median CL_{int} (μL/min/mg)	98	<47
Male rat hepatocytes median CL_{int} (μL/min/10^6 cells)	19	<27

The broad spectrum anti-trypanosomal activity of **3** attracted our attention as a modestly potent lead for HAT,

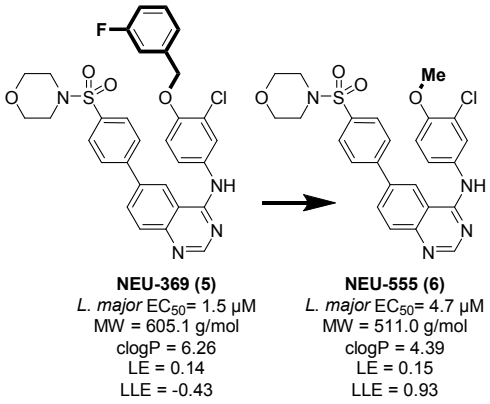
Chagas disease, and leishmaniasis. The primary shortcoming of **3** is in its poor predicated physicochemical properties, driven by a high molecular weight (569.6 g/mol) and clogP (5.76). Much of the MW and clogP of **3** may be attributed to the large, lipophilic 4-(3-fluorobenzyloxy)aniline "head group". We had previously observed that truncation of the similar 4-benzyloxy-3-chloroaniline group in our quinazoline series led only to a 3-fold loss in activity (*c.f.* **NEU-369**, **5** versus **NEU-555**, **6**, **Figure 2**).[14] Replacement of the 3-fluorobenzyl group with a methyl led to significant reductions in size (Δ HAC= -7) and lipophilicity (Δ clogP= -0.87), giving rise to a similar ligand efficiency (LE=pEC_{50}/heavy atom count, 0.14→0.15) and improved LLE (pEC_{50}-clogP, -0.43→0.93).[18-21]

Figure 1. SAR development of **NEU-1045** from lapatinib.



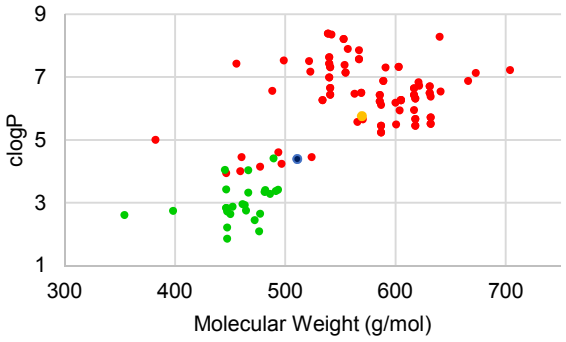
While the SAR of compounds built on the quinazoline scaffold were well explored[13] little attention had to this point been given to compounds built on the quinoline scaffold, despite their widespread prevalence as a privileged scaffold in medicinal chemistry.[22-24] When tested in a cross-parasite screening campaign, **3** inhibited *T. brucei*, *T. cruzi*, and *L. major* proliferation with good potency (*T. brucei* EC_{50}=0.37 μM; *T. cruzi* EC_{50}=2.8 μM; *L. major* EC_{50}=1.2 μM). We believed that reducing the molecular size and lipophilicity would lead to an improvement in the overall ADME profile of the series. As such, we hypothesized that smaller, more polar analogs built upon the **3** scaffold could lead to compounds that maintained antiparasite activity and were more soluble in water.

Figure 2. Truncation of lipophilic groups with partial retention of potency. All *L. major* data are in the intracellular amastigote life stage.



In order to accomplish our goal, we enumerated a virtual library of analogs of using JChem Reactor (ChemAxon, Inc.) and a set of 246 heterocyclic amines that are commercially available in pre-weighed quantities. Using Vortex (Dotmatics, Inc.) we shaped the library on the basis of clogP (<5) and molecular weight (<500). From this filtered virtual library of 132 compounds, we selected 23 analogs for synthesis via inspection, eliminating compounds with multiple reactive moieties, or those with anticipated difficulties in chemical stability or purification. Also selected for synthesis was the quinoline analog of **6**, bearing the truncated 3-chloro-4-methoxyaniline group that were featured in the active truncated analogs of **1** and **4**. Calculated physicochemical properties of these compounds in comparison with the properties of compounds previously described are plotted in **Figure 3**.[13-14]

Figure 3. Physicochemical properties analysis of lapatinib analogs selected after *in silico* enumeration and filtering. Related compounds that were previously disclosed are shown in red,[13-14] and the new shaped virtual library is shown in green. Compound **3** is shown in orange and **6** is shown in blue.

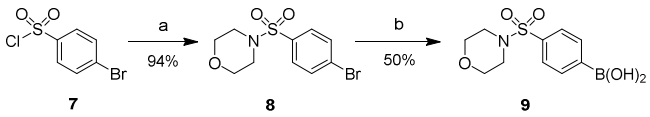


Chemistry

The synthesis of our selected library commenced with generation of the sulfonamide **8** from 4-bromophenylsulfonyl chloride, **7** (**Scheme 1**). Halogen-lithium exchange of **8** followed by quenching with tri-

*iso*propyl borate, and subsequent hydrolysis yielded boronic acid **9**.

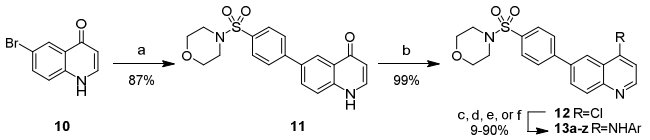
Scheme 1. NEU-1045 analog western half synthesis.



Reagents and conditions: (a) morpholine, THF, rt, o.n.; (b) *n*-BuLi, THF, -78 °C, 1 h; B(O*i*-Pr)$_3$ rt, o.n.; HCl rt.

Suzuki-Miyaura coupling of **9** and **10**[14] produced 6-arylquinolinone **11** (**Scheme 2**). Deoxychlorination of **11** generated **12** in nearly quantitative yield. Conversion to the corresponding 4-aminoquinolines **13a-z** could be achieved under acidic or basic conditions, or *via* Buchwald-Hartwig amination.

Scheme 2. NEU-1045 analog synthesis.



Reagents and conditions: (a) **9**, Et_3N, $Pd(PPh_3)_2Cl_2$, 1:1 EtOH/H_2O, ↓↑, 2 h; (b) $POCl_3$, ↓↑, 2 h; (c) TsOH, $ArNH_2$, DMSO, 80 °C, 24 h; (d) $ArNH_2$, Cs_2CO_3, $Pd_2(dba)_3$, xantphos, N_2, 1,4-dioxane, ↓↑, 24 h; (e) $ArNH_2$, KO*t*-Bu, $Pd_2(dba)_3$, xantphos, N_2, 1,4-dioxane, reflux, 24 h; (f) $ArNH_2$, NaH, 2:1 1,4-dioxane/DMF, 0→100 °C, 1 h.

Compounds were tested in an *in vitro* assay of RAW 246.7 macrophages infected with intracellular amastigotes of *L. major*, 3T3 fibroblasts infected with intracellular amastigotes of *T. cruzi*, and trypomastigotes of *T. brucei*. The data is summarized in **Table 2**. All compounds synthesized were also screened against *P. falciparum*, the causative agent of malaria (**Table S1**, supporting information). Compound toxicity to mammalian cells was assessed against HepG2 cells as well as NIH 3T3 cells (**Table S1**).

All analogs possessing a thiazole, isothiazole, or thiadiazole (**13l-p)** consistently maintained anti-leishmanial activity in the single digit micromolar range (1.2-5.4 μM). Compound **13v**, incorporating the truncated aniline of **6**, and the isostere **13k** also displayed activity in this range. The incorporation of nitrogen atom(s) into six-membered arenes was poorly tolerated against *L. major* amastigotes, with the exception of **13f** (EC_{50}=5.8 μM) and **13t** (EC_{50}= 0.37 μM).

Compound **13t** is of particular interest as the only compound in this library to achieve submicromolar activity against *L. major* amastigotes. Compound **13y**, devoid of an aminoheterocycle was inactive against all parasites tested, implicating these groups are essential structural motifs for antiparasitic activity. All compounds in this set were found to possess low host cell toxicities against HepG2 (TC_{50} >20 μM) except for **13k** (TC_{50}=9.0 μM).

Highlighted by **13t**, a dramatic improvement in LLE was achieved in this series (**13t** LLE=3.02, compared to **3**, LLE=0.16) driven by the reduced clogP (**13t**=3.41, **3**=5.76, **Table S2**, Supporting Information). Despite the improved lipophilicity profile, aqueous solubility (1 μM) and PPB (99.6%) remained poor. Taken together, these properties limited these compounds' progression to further studies against *Leishmania*.

Noting that the targeted potency range for anti-*T. cruzi* lead compounds is <10 μM,[25] we were pleased to observe that approximately half of the compounds tested showed some activity against *T. cruzi,* with six in the single digit micromolar range. The most potent were **13k** (EC_{50}=3.6 μM) and **13o** (EC_{50}=3.9 μM). Importantly, we observed all compounds were non-toxic to NIH 3T3 host cells (TC_{50} >20 μM) with the exception of **13k** (TC_{50}=15 μM).

Sixteen analogs showed activity in the 1-10 μM range against *T. brucei*, and an additional six were <1 μM, including the highly active **13o** (EC_{50}=72 nM) and **13j** (EC_{50}=24 nM). We were intrigued by the activity of **13j** against *T. brucei.* Compared to **3**, **13j** has a lower molecular weight (447.5 vs. 569.6 g/mol) and clogP (2.72 vs. 5.76; **Table S2**, Supporting Information), reflected in the improved LE (0.24) and excellent LLE (4.9). This compound showed an acceptable $logD_{7.4}$ (3.3), and improvement in human plasma protein binding (95.6%), though the thermodynamic aqueous solubility remained poor (1.4 μM).

We note that, despite the similarity between the kinomes of the three kinetoplastid parasites, we see distinct differences in selectivity across species. There are some potential explanations for this. First, though homologous across pathogens, certain targets may not have similar essentiality. Second, there are potential confounding factors involved by virtue of the nature of the parasite (intra- versus extra-cellular), and there could be potentiating effects from host cell targets. We do note, however, that we do not know the target(s) of action for these compounds; this is of interest for future work.

Given the attractive potency and drug-like properties of **13j**, we performed pharmacokinetic experiments in mice. Compound **13j** was dosed by intraperitoneal injection to 18 female BALB/c mice at 10 mg/kg. Blood and brain samples were collected from groups of 3 at 0.08, 0.25, 1, 4, 8, and 24 h and analyzed by LC-MS/MS. The results are visualized in **Figure S1** and tabulated in **Tables S3-S6** in the supporting information. We observed plasma exposure >120-fold of the EC_{50} for 4 h, and the maximum brain to plasma ratio was 0.01 at 0.25 h after dosing **13j**. In conjunction with the low levels of **13j** in the brain, we noted the rapid clearance in human liver microsomes (Cl_{int}=207.5 μL/min/mg) and rat hepatocytes (Cl_{int}=31.5 μL/min/10^6 cells) suggested **13j** would show poor efficacy in *in vivo* models of infection. We continue to work towards compounds with improved PK properties, and will report these results in due course.

In summary, through a strategy of generation and filtering of a virtual library of analogs of **3** on the basis of computed physicochemical properties, we have identified potent inhibitors of *L. major, T. cruzi,* and *T. brucei* proliferation. These compounds possess improved drug-like properties and efficiency metrics as a result, in part, of the re-

duction in molecular weight and lipophilicity designed in the virtual library. Further work aimed at improving the *in vivo* ADME properties and requisite properties for the different protozoan parasites will be undertaken. In addition, attention must be paid to the non-parallel SAR that we have observed between parasites. As a result, a single, multi-pathogen-targeting agent would seem unlikely, and pathogen-specific optimization is needed at this point.

ASSOCIATED CONTENT

Supporting Information

Chemical synthesis and characterization of new compounds reported, antimalarial and physicochemical property data tables (annotated with NEU registry numbers), and biological methods. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

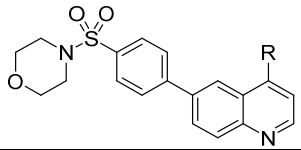
Funding Sources

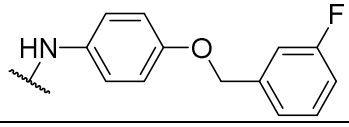
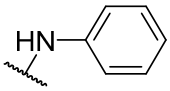
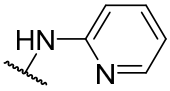
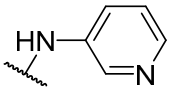
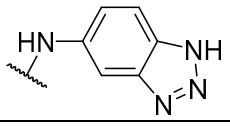
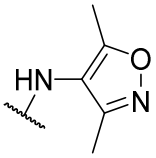
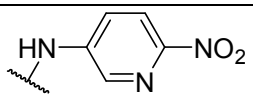
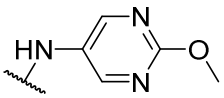
Funding from the National Institutes of Health (R01AI124046 and R56AI099476 to M.P.P. and K.M.-W.) and Northeastern University are gratefully acknowledged.

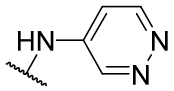
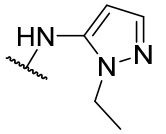
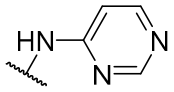
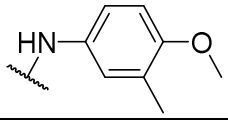
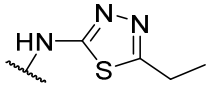
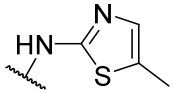
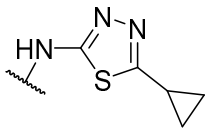
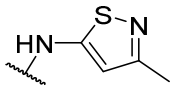
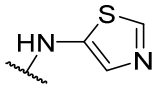
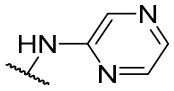
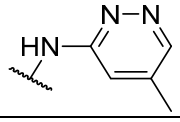
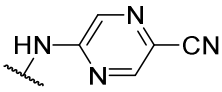
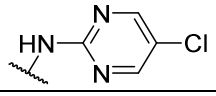
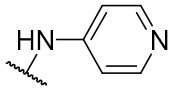
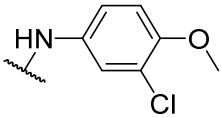
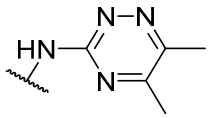
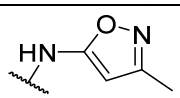
ACKNOWLEDGMENT

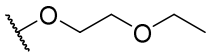
ChemAxon is gratefully acknowledged for the free academic license provided for their software suite. Dr. Lori Ferrins is gratefully acknowledged for her assistance in preparing this manuscript. We are grateful to AstraZeneca for the determination of *in vitro* ADME properties in support of this work.

Table 2. Anti-kinetoplastid activity of analogs of compound 3.



Cmpd	R	*L. major*		*T. b. brucei*		*T. cruzi*	
		EC_{50} (μM)[a,c]	LLE	EC_{50} (μM)[b]	LLE	EC_{50} (μM)[b]	LLE
3		1.2	0.16	0.37[c]	0.67	2.8[d]	-0.21
13a		7.1	1.1	0.98	2.0	6.2	1.2
13b		>20		4.5	1.9	16	1.4
13c		>20		3.8	2.6	>20	
13d		>20		16	1.5	>20	
13e		>20		6.6	2.4	>20	
13f		5.8	1.9	3.2	2.1	>20	
13g		>20		5.6	2.6	>20	

13h		>20		>20		>20	
13i		>20		2.5	2.7	>20	
13j		>20		0.024	4.9	>20	
13k		5.7	0.83	0.31	2.1	3.6	1.0
13l		3.1	2.2	4.2	2.0	>20	
13m		1.2	1.9	1.6	1.8	6.1	1.2
13n		2.0	2.3	4.7	1.9	>20	
13o		4.5	2.0	0.072	3.8	3.9	2.1
13p		5.4	2.4	1.2	3.0	>20	
13q		>20		>20		>20	
13r		>20		2.0	2.7	>20	
13s		>20		7.9	2.7	>20	
13t		0.37	3.0	3.8	2.0	>20	
13u		>20		0.11	4.1	>20	
13v		5.3	0.78	1.7	1.3	7.2	0.64
13w		>20		3.1	3.4	>20	
13x		>20		1.1	3.3	7.6	2.5

13y*	H	>20		>20		>20	
13z*		>20		0.71	3.4	>20	

[a] All r^2 values >0.75. [b] All SEM values within 25%. [c] n=1. [d] n=2. *Isolated as a side product.

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Antiparasitic Lead Discovery: Towards Optimization of a Chemotype with Activity Against Multiple Protozoan Parasites

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