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Research paper

Synthesis and trypanocidal activity of a library of 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols

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ABSTRACT

A library of 16 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols **17**–**32** has been synthesized for use in biological testing against *Trypanosoma cruzi*, the protozoan parasite that causes Chagas disease. The 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols **17**–**32** were subjected to biological testing to evaluate their efficacy against intracellular *Trypanosoma cruzi* (Y strain) amastigotes infecting U2OS human cells, with benznidazole as a reference compound. The assay was performed in duplicate (two independent experiments) and submitted to High Content Analysis (HCA) for determination of trypanocidal activity. Three of the tested compounds presented relatively high trypanocidal activity (**19**, **22** and **29**), however severe host cell toxicity was observed concomitantly. Chemical optimization of the highly active compounds and the synthesis of more compounds for biological testing against *Trypanosoma cruzi* will be required to improve selectivity and so that a structure-activity relationship can be generated to provide a more insightful analysis of both chemical and biological aspects.

1. Introduction

Chagas disease, also known as American trypanosomiasis, is a chronic infectious disease endemic in Latin America. The disease is caused by the protozoan parasite *Trypanosoma cruzi*, which is transmitted to humans by blood-sucking triatomine insect vectors. Other forms of contagion are organ transplant or blood transfusion contaminated with *Trypanosoma cruzi*, transmission from mother to fetus during pregnancy (vertical transmission), or by ingestion of food or drink contaminated with live parasites [1]. The World Health Organization estimates that there are approximately 7 million people who are infected with *Trypanosoma cruzi* in the world, and although Chagas disease is endemic in Latin America, global migratory phenomena has scattered infected individuals to several non-endemic countries, including USA, Canada, Spain Australia and Japan, where parasite transmission can occur, especially for organ transplantation and transfusion of contaminated blood, since the practice of screening for *Trypanosoma cruzi* in blood and organ banks is not common in these countries [2]. It is estimated that in the United States alone there are about 300 thousand infected individuals, and a recent study suggests that a cycle of transmission of *Trypanosoma cruzi* is occurring locally [3]. Chagas disease begins when an individual becomes infected with *Trypanosoma cruzi*. Transmission by vector occurs when triatomines deposit infected faeces near the site of the bite, the bite of which compromises the physical integrity of the skin. The bite induces an inflammatory reaction that causes itching so that when the individual scratches the site of the bite the contaminated faeces are spread to the bite, allowing the parasite to penetrate the bite lesion (or the parasites can be spread to the mucous membranes, such as the eyes, where the parasites can easily enter).

The transmission form of the parasite is called the trypomastigote, and is capable of infecting various cells in the host organism. Once inside the cells the trypomastigotes differentiate into amastigotes, which are intracellular forms that are able to multiply. After a few days, the amastigotes differentiate into trypomastigotes and disrupt the host cell by moving in a tumbling fashion, they then go on to infect new cells, thus establishing the infection in the host.

The initial period of infection (acute phase) is characterized by non-specific symptoms such as fever, and diagnosis often fails due

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to the generality of the symptoms. If Chagas disease is not treated during the acute phase, the disease progresses to a chronic phase, which is also known as the indeterminate phase.

This may be asymptomatic and is the most common clinical presentation. Decades after infection, about 30% of patients develop the cardiac form of the disease, which is characterized by progressive injury to the heart muscle tissue, causing arrhythmias and cardiac failure. Some patients develop the digestive form of Chagas disease, which is characterized by loss of muscle motility in the digestive tract [4]. For many years, medical scientists thought that there was an autoimmune component involved in Chagas disease. It is now known that pathological lesions occur due to the persistence of the parasite in infected tissues and therefore it is recommended that patients receive antiparasitic treatment at any stage of disease [5].

Because it is a disease that affects mainly economically disadvantaged populations in developing countries, there has been little interest in the pharmaceutical industry to develop new therapies for the treatment of Chagas disease and therefore Chagas disease is considered a neglected disease. Currently there are only two drugs available for clinical use: the nitroimidazole compound benznidazole and the nitrofuran compound nifurtimox. Both were developed about 40 years ago and belong to the class of compounds called nitroheterocyclics, which usually deliver broad-spectrum antimicrobial activity, but with high toxicity [6].

Both drugs require prolonged administration (about 60 days) and have high efficacy and curative rate when administered during the acute phase of infection. The use of benznidazole or nifurtimox for the treatment of symptomatic chronic Chagas patients is still considered controversial. Although both exhibit antiparasitic efficacy, both are associated with substantial side effects, which often lead to the abandonment of the treatment by the patient, and are contraindicated in some circumstances, such as during pregnancy [7]. Therefore, benznidazole and nifurtimox are not satisfactory drugs and new approaches are needed for the treatment of Chagas disease.

Thus a continuous search for new drugs is required to ensure the discovery and development of alternatives to current drugs. Thankfully research in the development and testing of antitrypanosomal/trypanocidal compounds has never abated, recent examples include the 2-((4,5-disubsituted-thiazol-2-yl)amino)isoindoline-1,3-diones, 2-((E)-2-((Z)-(3,4-disubsituted-thiazol-2(3H)-ylidene)hydrazono)ethyl)isoindoline-1,3-diones, (E)-2-(2-(1-(3-bromophenyl)propylidene)hydrazinyl)-4,5-disubstituted-thiazoles and (Z)-2-((E)-(1-(3-bromophenyl)propylidene)hydrazono)-3,4,5-trisubstituted-2,3-dihydrothiazoles developed and tested by Moraes Gomes et al. [8], and the nitrotriazole-based acetamides and propanamides developed and tested by Papadopoulou et al. [9].

Trypanosoma species express several kinases, an observation that has driven efforts to identify classes of kinase inhibitors that can be useful for discovery of new parasite growth inhibitors. To identify new kinase-targeting chemotypes for target and pathway analysis and drug discovery for *Trypanosoma brucei* (the causal pathogen of human African trypanosomiasis (HAT) and related to *Trypanosoma cruzi*) Diaz et al. performed a high-throughput screen of 42,444 focused inhibitors, from the GlaxoSmithKline screening collection, against parasite cell cultures and counter-screened against human hepatocarcinoma (HepG2) cells. They identified hundreds of compounds that ranged in performance from being (1) sub-micromolar (EC_{50}) inhibitors of *T. brucei* growth with at least 100-fold selectivity over HepG2 cells, (2) hit compounds that rapidly inhibited cellular growth, and (3) compounds that showed rapid cidality. Compounds **1**–**9** (Fig. 1) were among the best performing and showed pEC_{50}s of 6.16–9.17 and pTC_{50}s of <4–4.84. Compounds **1**–**9** were also fast acting ($pEC_{50} \geq 6$ at 18 h) and cidal. The best compound tested, NEU-0001053 **7**, demonstrated parasitological cure of a murine bloodstream infection of *T. brucei rhodesiense* [10].

Woodland et al. recently performed a screen of a focused kinase inhibitor library against *Trypanosoma brucei rhodesiense* leading to the identification of several compounds (seven series, 121 in total) which showed >50% inhibition at 5 μM. Screening of these compounds in a *T. b. brucei* proliferation assay identified three compounds with the 1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one ring system or scaffold that showed sub-micromolar activity and excellent selectivity against the MRC5 cell line. Subsequent rounds of optimization with synthetic chemistry and biological testing led to the identification of compounds that exhibited good in vitro drug metabolism and pharmacokinetics (DMPK) properties, albeit with poor solubility. A scaffold-hopping exercise, involving more synthetic chemistry and biological testing, led to the identification of a 1*H*-pyrazolo[3,4-*b*]pyridine scaffold, which retained potency. A number of these compounds were tested in a *T. b. brucei* growth assay, which could differentiate static (growth slowing/inhibiting) and cidal action. Compounds from the 1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one series were found to be either static or growth-slowing and not cidal, whereas compounds with the 1*H*-pyrazolo[3,4-*b*]pyridine scaffold, such as compounds **10** and **11** (Fig. 2), were found to be cidal and showed an unusual biphasic nature in the assay, suggesting that they act by at least two mechanisms [11]

The potent and selective antitrypanosomal/trypanocidal compounds shown in Figs. 1–2 all contain a variety of different fused bicyclic heteroarenes, namely 1*H*-pyrrolo[2,3-*b*]pyridine, 1*H*-benzo[*d*]imidazole, indole, furo[2,3-*d*]pyrimidine and 1*H*-pyrazolo[3,4-*b*]pyridine, with monocyclic substituents such as aryl, heteroaryl and cycloalkyl attached. Drawing inspiration from the antitrypanosomal/trypanocidal compounds shown in Figs. 1–2, we wondered whether 1*H*-pyrrolo[3,2-*c*]pyridines (5-azaindoles), which are not represented in these literature examples, would also show antitrypanosomal/trypanocidal activity, perhaps by inhibition of trypanosomal kinases. Therefore, for this work we synthesized a library of differently substituted 1*H*-pyrrolo[3,2-*c*]pyridines (5-azaindoles) and subjected them to biological testing against *Trypanosoma cruzi*, the causal pathogen of Chagas disease.

2. Results and discussion

2.1. Synthetic chemistry

The precursor compound for the synthesis of the library, 2-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ol **16**, was synthesized in four steps from commercially available 2-chloropyridin-4-amine **12**. 2-Chloropyridin-4-amine **12** was iodinated with iodine monochloride in glacial acetic acid, in the presence of sodium acetate trihydrate, with heating at 70 °C. This produced the desired 2-chloro-3-iodopyridin-4-amine **13** in 45% yield [12]. The 2-chloro-3-iodopyridin-4-amine **13** was then bis-mesylated with methanesulfonyl chloride in anhydrous pyridine at room temperature, according to the procedure of Sakamoto et al. [13]. This produced *N*-(2-chloro-3-iodopyridin-4-yl)–*N*-(methylsulfonyl)methanesulfonamide **14** in 89% yield. Then **14** was monodemesylated with 2.75 M aqueous sodium hydroxide in tetrahydrofuran at room temperature, which produced the desired monomesylate *N*-(2-chloro-3-iodopyridin-4-yl)methanesulfonamide **15** in 87% yield [12b], [12c]. This set the stage for the key cyclization which would form the desired 1*H*-pyrrolo[3,2-*c*]pyridine (5-azaindole) ring system. Very few examples of the synthesis of substituted 1*H*-pyrrolo[3,2-*c*]pyridines have been reported over the years. Miscellaneous synthetic methods have been reported for the preparation of substituted indoles [13], [14], but relatively few have

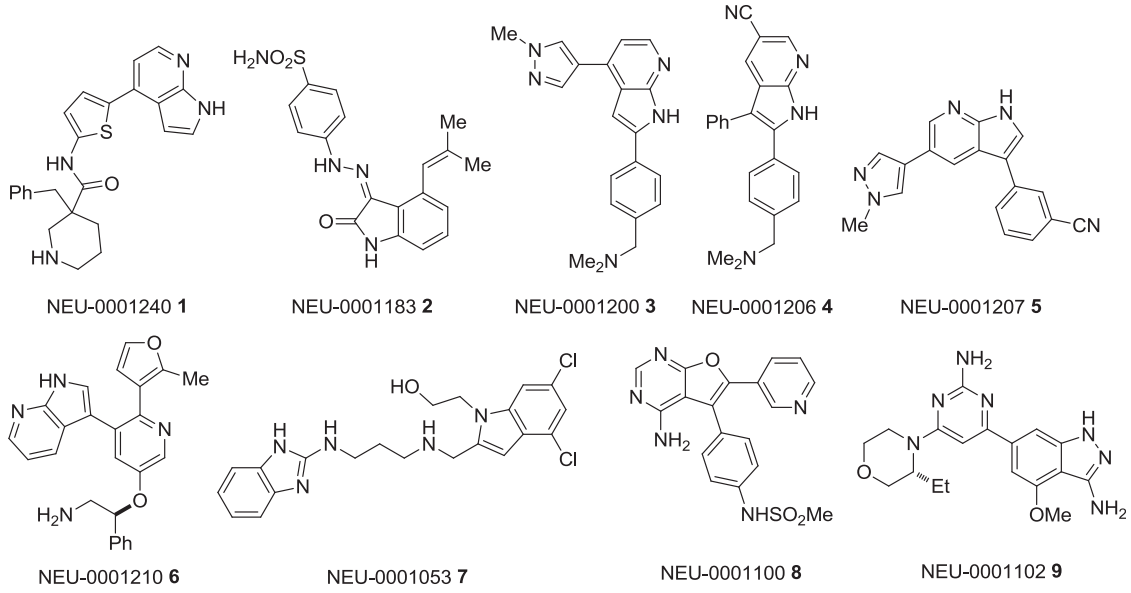


Fig. 1. Structure of the trypanocidal compounds discovered by Diaz et al. [10].

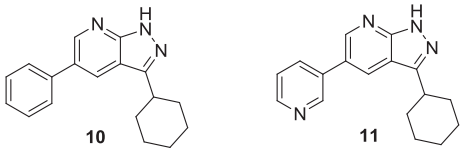


Fig. 2. The two most potent and trypanocidal 1*H*-pyrazolo[3,4-*b*]pyridine compounds discovered by Woodland et al. [11].

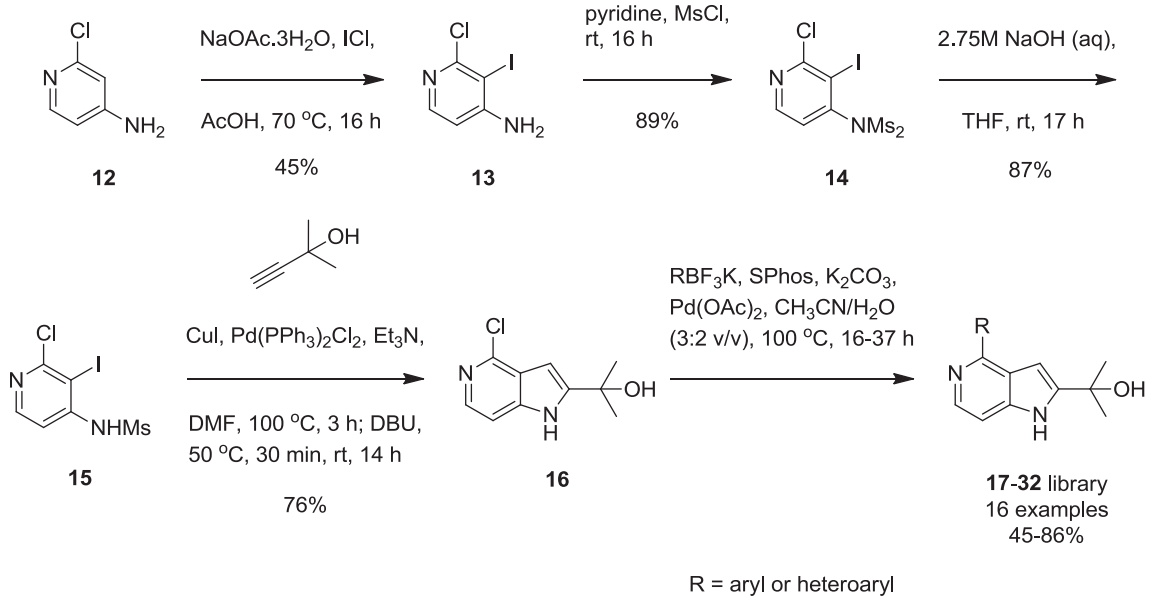
been applied to the preparation of substituted 4-, 5- and 6-azaindoles [15]. This fact could be explained by the high electron affinity of the pyridine ring system. The presence of the nitrogen atom in the pyridine ring alters the electronics of the π-system in such a way that many classical indole formation methods do not work or are not efficient [16]. However, literature examples by Hu et al. [12c], the patent WO 2014/207260 A1 [12b] and Choi-Sledeski et al. [17] showed that the desired 1*H*-pyrrolo[3,2-*c*]pyridine (5-azaindole) ring system could be formed with a tandem Sonogashira coupling/5-endo-dig cyclization involving compound **15** or similar *N*-sulfonylated or *N*-acylated 3-iodopyridin-4-amines and various terminal alkynes. Inspired by these precedents in the literature, we coupled *N*-(2-chloro-3-iodopyridin-4-yl)methanesulfonamide **15** and 2-methyl-3-butyn-2-ol with a Sonogashira coupling reaction (CuI, $PdCl_2(PPh_3)_2$, Et_3N, DMF), heated at 100 °C for 3 h. The reaction mixture was then cooled to 50 °C and DBU was added. Heating at 50 °C was continued for 30 min and then the reaction was left at room temperature overnight. As predicted by the literature, the desired tandem Sonogashira/5-endo-dig cyclization occurred and produced the desired cyclized compound 2-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ol **16** in 76% yield, with concomitant demesylation (Scheme 1) (see Fig. 3).

The library of 16 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols **17**–**32** was then synthesized from 2-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ol **16** with a variant of the Suzuki-Miyaura coupling reaction that was developed by Buchwald. The general procedure for this Suzuki-Miyaura coupling reaction involved coupling 2-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ol **16** with various different potassium organotrifluoroborates (1.5 equiv each) in the presence of dicyclohexyl(2′,6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (SPhos) (0.025 equiv), potassium carbonate (3.0 equiv), palladium(II) acetate (0.1 equiv) and with acetonitrile/water (3/2 v/v, conc 0.1 M (acetonitrile), conc 0.15 M (water)) as the reaction solvent [18]. The yields ranged from 45 to 86%, although some of the low yields may well have been due to the need to perform several sessions of flash column chromatography to achieve purity. Indeed the main impurity was found to be residual SPhos. In later experiments the stoichiometry of the SPhos was reduced to 0.025 equiv to ensure easy chromatographic purification of the 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols.

The Suzuki-Miyaura coupling reactions that employed potassium (4-bromophenyl), (4-formylphenyl), 3-aminophenyl, 3-nitrophenyl, 4-carboxyphenyl, 2,6-dimethoxyphenyl, 2-methylphenyl, 4-aminocarbonylphenyl, 4-hydroxymethylphenyl or (5-methylthiophen-2-yl) trifluoroborate salts or ferrocene boronic acid all failed, resulting in either the presence of unreacted starting material 2-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl) propan-2-ol **16** and no detectable product, 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ol, or the destruction of the 2-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ol **16** starting material and the formation of a complex mixture of unidentifiable products, according to tlc and GC/MS (EI).

2.2. Biological studies

The biological testing was performed as described in Moraes et al. 2014 [1923] and is described in detail in the experimental section and Supplementary information. Some of the tested compounds presented relatively high antiparasitic activity yielding EC_{50} values in the low micro molar range (EC_{50} < 10 μM), such as compounds 19 (4-(2-fluoro-(1,1'-biphenyl)-4-yl) substituted), 22 (4-(4-(ethylthio)phenyl) substituted) and 29 (4-((4-(benzyloxycarbonylamino)phenyl) substituted) (Table 1 and Supplementary Fig. 1). On the other hand, the selectivity towards host cell was not sufficiently high to proceed into further studies. Interestingly, compounds 19 and 29 displayed high efficacy, comparable to that of the reference compound, benznidazole. Compounds 18, 20–21, 24–25, 28 and 30–32 exhibited moderate or low potency when compared with the other tested compounds; moreover, these compounds presented poor selectivity indices due to high cell



Scheme 1. Synthesis of 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols **17**–**32**.

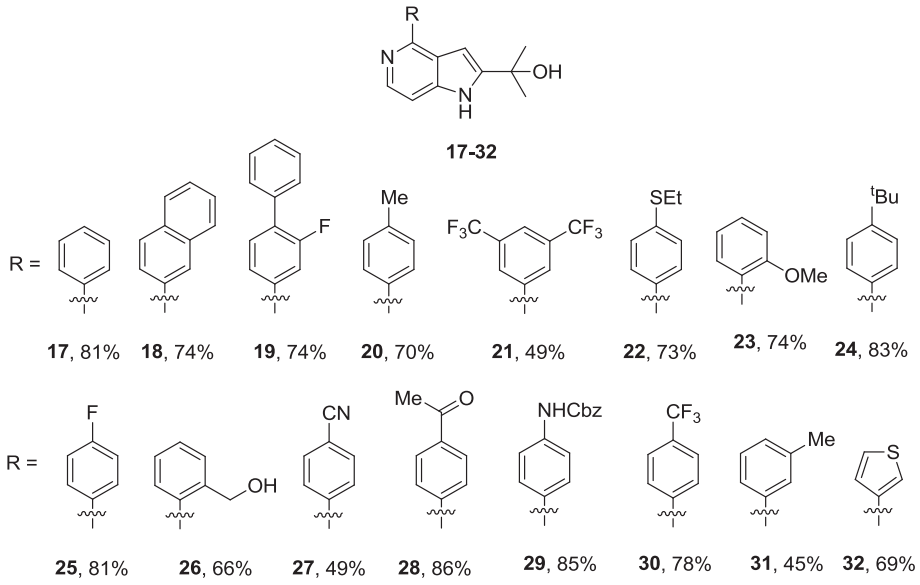


Fig. 3. The library of 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols **17**–**32**.

toxicity, except for 23 (see Fig. 4).

With regards to the interplay between the synthetic chemistry and the biological testing, the Suzuki-Miyaura coupling reaction with the chloro-substituted compound **16** was, as already mentioned, quite limited. Only 16 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols (**17**–**32**) could be synthesized, even though a total of 27 different potassium organotrifluoroborates or boronic acids were tried with the Suzuki-Miyaura coupling reaction. This meant that not enough library compounds were available for structure-activity relationship experiments to be conducted. Despite that this work still revealed that 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols with 2-fluoro-(1,1'-biphenyl)-4-yl (**19**), 4-(ethylthio)phenyl (**22**) and 4-(benzyloxycarbonylamino)phenyl (**29**) show some antitrypanosomal activity and could form the basis of chemical structure optimization to increase anti-trypanosomal activity and selectivity. Future work will focus on increasing the scope of the Suzuki-Miyaura coupling reaction, as well as the scope of the tandem Sonogashira coupling/5-endo-dig cyclization, so that variation can be achieved on two sides of the molecule, so that in turn a wider variety of library compounds can be synthesized for further biological testing, for performing structure-activity relationship experiments and to test for trypanosomal kinase inhibition.

3. Conclusion

A library of 16 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl) propan-2-ols **17**–**32** has been synthesized for use in biological testing against *Trypanosoma cruzi*, the protozoan parasite that causes Chagas disease. The immediate precursor compound to the

Table 1
EC_{50}, Maximum Activity, CC_{50}, and Selectivity Index (SI) of new and reference compounds against Y strain *Trypanosoma cruzi* intracellular amastigotes.

Entry	EC_{50} (μM)	SD	CC_{50} (μM)	SD	Max. Activ. (%)	SI
Benznidazole	3.6	1.3	–	–	102.3	>235
16	70.8	17.7	15.5	5.8	106	0.2
17	6.5	3.3	22.2	4.5	106	3.4
18	20.1	1.1	22.5	2.2	102	1.1
19	3.8	1.2	9.1	1.1	75.7	2.4
20	34.6	5.5	38.5	0.9	86	1.1
21	24.3	1.3	59.8	13.3	72.2	2.5
22	9.6	0.03	17.2	9.1	106.8	1.8
23	53.9[a]	–	–	–	56.6	>3.7
24	17	11.9	35.3	1.8	110	1.3
25	45.8	7	93.6	9	75.8	2.0
26	–	–	–	–	30.1	–
27	–	–	–	–	30.6	–
28	137	2.3	–	–	60.9	>1.4
29	4.5	1.3	5.5	1.3	99.4	1.22
30	40.9	12.9	72.3	8.3	102.4	1.5
31	52.3	12.3	121	15.5	100.7	1.7
32	106	24.7	199	1.4	72.8	1.6

Average values of two replicates are shown; SD = Standard Deviation.
- indicates the value could not be calculated.
[a] Indicates that the value was obtained in a single replicate.

library, 2-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ol **16**, was synthesized in four steps from commercially available 2-chloropyridin-4-amine **12** with a tandem Sonogashira/5-endo-dig cyclization (**15** → **16**) as a critical step for forming the desired 1*H*-pyrrolo[3,2-*c*]pyridine (5-azaindole) ring system of the 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols **17**–**32**. The synthesis of the library compounds **17**–**32** was completed by using a variant of the Suzuki-Miyaura coupling reaction, developed by Buchwald, to couple 2-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl) propan-2-ol **16** with various different potassium organotrifluoroborates. The 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols **17**–**32** were subjected to biological testing to evaluate their efficacy against intracellular *Trypanosoma cruzi* (Y strain) amastigotes infecting U2OS human cells, with benznidazole as a reference compound. The assay was performed in duplicate (two independent experiments) and submitted to High Content Analysis (HCA) for determination of trypanocidal activity. Three of the tested compounds presented relatively high trypanocidal activity (**19**, **22** and **29**), however severe host cell toxicity was observed concomitantly. Chemical optimization of the highly active compounds and the synthesis of more compounds for biological testing against *Trypanosoma cruzi* will be required to improve selectivity and so that a structure-activity relationship can be generated to provide a more insightful analysis of both chemical and biological aspects.

4. Experimental section

4.1. Synthetic chemistry

4.1.1. General considerations

Unless stated otherwise all reactants and reagents were obtained from commercial sources and used without further purification. All solvents were distilled before use. Tetrahydrofuran was distilled from sodium and benzophenone, methanesulfonyl chloride was distilled from phosphorus pentoxide under vacuum, pyridine and triethylamine were distilled from calcium hydride under vacuum and atmospheric pressure respectively and *N*,*N*-dimethylformamide was distilled from magnesium sulfate under vacuum. Air and moisture-sensitive reactions were conducted in flame-dried or oven dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry nitrogen. Reagents and solvents were handled using standard syringe and graduated pipette techniques. Thin layer chromatography (TLC) was performed using silica gel UV_{254} 0.20 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine, or acidic vanillin solution. Column chromatography was performed using silica gel (230–400 mesh). ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained with a Bruker Avance DPX 300 spectrometer with complete proton decoupling. Data is reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$/acetone-d6, referenced to the solvent peak of $CDCl_3$ or acetone-d6; multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, td = triplet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, br = broad); coupling constants (*J*) in Hertz and integrations. Infrared (IR) spectra were obtained with an Agilent Technologies Cary 630 FTIR spectrometer. High resolution mass spectra (HRMS) were obtained with a Shimadzu ESI-IT-ToF mass spectrometer. Autosampler injection was performed in 50% acetonitrile, containing 0.1% acetic acid and the sample was analyzed under positive ionization mode (ESI+). The interface voltage was kept at 4.5 kV, the detector voltage at 1.70 kV and the capillary temperature at 200 °C. The mass range used was 50–1850 *m*/*z*. Instrument control, data acquisition and processing was performed with the Lab Solution/LC-MSsolution Suite from Shimadzu. Low resolution gas chromatograph/mass spectrometry electron impact (GC/MS (EI)) spectra were obtained with a Shimadzu GC-17A gas chromatograph connected to a Shimadzu GCMS-QP5050A gas chromatograph/mass spectrometer. Melting points were obtained with a Buchi Melting Point B-545 apparatus and are uncorrected.

4.1.2. Syntheses

*4.1.2.1. 2-Chloro-3-iodopyridin-4-amine **(13)**.* A 50 mL single necked round bottom flask equipped with a magnetic stirrer bar, reflux condenser and nitrogen line was charged with 2-chloropyridin-4-amine **12** (2.50 g, 19.4 mmol, 1.0 equiv), sodium acetate trihydrate (3.97 g, 29.2 mmol, 1.5 equiv), iodine monochloride (3.47 g, 21.4 mmol, 1.1 equiv) and glacial acetic acid (13.0 mL) and heated at 70 °C with magnetically facilitated stirring under nitrogen for 16 h, at which point tlc and GC/MS (EI) analysis showed that the starting material had been consumed. The reaction mixture was cooled and transferred to a separating funnel where it was carefully quenched with portion wise addition of solid powdered sodium hydrogencarbonate (32.3 g), water (75 mL) and ethyl acetate (75 mL). The resultant effervescence was allowed to subside and the mixture was not shaken. The layers were then separated and the aqueous layer was extracted with ethyl acetate (6 × 25 mL), with shaking. The organic layers were combined and dried over magnesium sulfate and the solvent was removed *via* rotary evaporation. The residue was purified by portionwise flash column chromatography over silica using *n*-hexane/ethyl acetate (94:6 to 60:40) mixtures as eluent to give 2-chloro-3-iodopyridin-4-amine **13** as a light brown solid (2.21 g, 45%), a sample of which had ^1H NMR spectral data and low resolution GC/MS (EI) mass spectral data identical to those in the literature [12].

*4.1.2.2. N-(2-Chloro-3-iodopyridin-4-yl)–N-(methylsulfonyl)methanesulfonamide **(14)**.* A 50 mL single necked round bottom flask equipped with a magnetic stirrer bar and nitrogen line was charged with 2-chloro-3-iodopyridin-4-amine **13** (3.08 g, 12.1 mmol, 1.0 equiv), pyridine (24 mL) and methanesulfonyl chloride (6.93 g, 4.68 mL, 60.5 mmol, 5.0 equiv), the last two being added via graduated pipette, all at room temperature. The reaction mixture was stirred (magnetically facilitated) at room temperature under

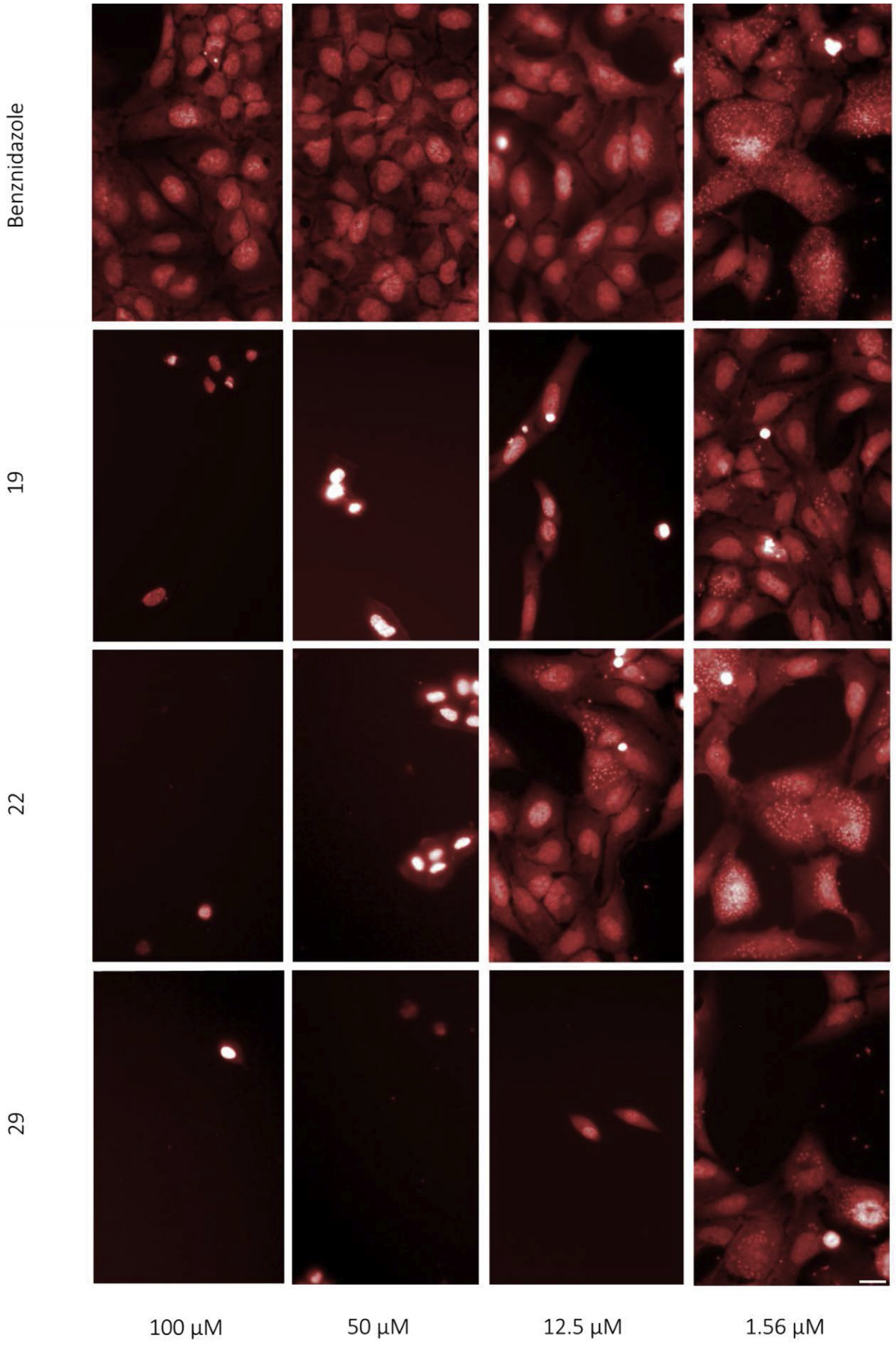


Fig. 4. Representative images obtained from Operetta High Content System (20× WD objective - Draq5 DNA staining) reveal distinct anti-*T. cruzi* activity and U2OS host cell variable tolerability towards reference compound benznidazole and three top-rate-activity compounds: **19**, **22** and **29** at four different concentrations: 100, 50, 12.5 and 1.56 µM. Bar: 20 µm.

nitrogen for 16 h at which point tlc analysis showed that the starting material **13** had been consumed. GC/MS (EI) analysis was not particularly informative for assessing the progress of this reaction. The reaction mixture was transferred to a separating funnel with the assistance of ethyl acetate (50 mL) and water (50 mL). The mixture was shaken, the layers were separated and the aqueous layer was extracted with ethyl acetate (10 × 25 mL), with shaking. The organic layers were combined and dried over magnesium sulfate and the solvent was removed via rotary evaporation. The residue was purified by flash column chromatography over silica using n-hexane/ethyl acetate (97:3 to 50:50) mixtures as eluent to give *N*-(2-chloro-3-iodopyridin-4-yl)–*N*-(methylsulfonyl)methanesulfonamide **14** as a light brown solid (4.32 g, 89%), a sample of which had ^{1}H NMR spectral data and low resolution GC/MS (EI) mass spectral data identical to those in the literature [12b,c,13].

*4.1.2.3. N-(2-Chloro-3-iodopyridin-4-yl)methanesulfonamide **(15)**.* A 50 mL single necked round bottom flask equipped with a magnetic stirrer bar and nitrogen line was charged with *N*-(2-chloro-3-iodopyridin-4-yl)–*N*-(methylsulfonyl)methanesulfonamide **14** (1.59 g, 3.88 mmol, 1.0 equiv), tetrahydrofuran (31 mL) and aqueous sodium hydroxide solution (2.75 M, 8.47 mL, 23.3 mmol, 6.0 equiv), the last two being added via measuring cylinder, all at room temperature. The reaction mixture was stirred (magnetically facilitated) at room temperature under nitrogen for 17 h at which point tlc analysis showed that the starting material **14** had been consumed. GC/MS (EI) analysis was not particularly informative for assessing the progress of this reaction. The reaction mixture was transferred to a separating funnel with the assistance of ethyl acetate (50 mL) and water (100 mL). The mixture was shaken, the layers were separated and the aqueous layer was extracted with ethyl acetate (10 × 50 mL), with shaking. The organic layers were combined and dried over magnesium sulfate and the solvent was removed via rotary evaporation. The residue was purified by flash column chromatography over silica using n-hexane/ethyl acetate (92:8 to 40:60) mixtures as eluent to give *N*-(2-chloro-3-iodopyridin-4-yl)methanesulfonamide **15** as a light yellow solid (1.12 g, 87%), a sample of which had ^{1}H NMR spectral data and low resolution GC/MS (EI) mass spectral data identical to those in the literature [12b,c].

*4.1.2.4. 2-(4-Chloro-1H-pyrrolo[3,2-c]pyridin-2-yl)propan-2-ol **(16)**.* A 25 mL single necked round bottom flask (the reaction vessel) equipped with a magnetic stirrer bar, reflux condenser and nitrogen line was charged with *N*-(2-chloro-3-iodopyridin-4-yl)methanesulfonamide **15** (982 mg, 2.95 mmol, 1.0 equiv), copper(I) iodide (11.3 mg, 59.1 μmol, 0.02 equiv) and dichlorobis(-triphenylphosphine)palladium(II) (41.5 mg, 59.1 μmol, 0.02 equiv) and placed under nitrogen, all at room temperature. Triethylamine (1.20 g, 1.65 mL, 11.8 mmol, 4.0 equiv) and *N*,*N*-dimethylformamide (2.95 mL), in a separate 25 mL single necked round bottom flask, was degassed with three freeze-pump-thaw cycles. The degassed triethylamine/*N*,*N*-dimethylformamide was then added to the reaction vessel via a pipette. Then 2-methyl-3-butyn-2-ol (373 mg, 429 μL, 4.43 mmol, 1.5 equiv) was added via graduated pipette, all at room temperature. The reaction mixture was then heated at 100 °C under nitrogen with magnetically facilitated stirring for 3 h, at which point tlc and GC/MS (EI) analysis showed that the starting material **15** had been consumed. The reaction mixture was cooled to 50 °C and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (899 mg, 884 μL, 5.91 mmol, 2.0 equiv) was added via graduated pipette. The reaction mixture was heated at 50 °C for 30 min and then at room temperature for 14 h. The reaction mixture was transferred to a separating funnel with the assistance of ethyl acetate (25 mL) and water (25 mL). The mixture was shaken, the layers were separated and the aqueous layer was extracted with ethyl acetate (5 × 25 mL), with shaking. The organic layers were combined and dried over magnesium sulfate and the solvent was removed *via* rotary evaporation. The residue was purified by flash column chromatography over silica using *n*-hexane/ethyl acetate (99:1 to 0:100) mixtures as eluent to give 2-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ol **16**: [12b,c,13,17] Light brown solid, 472 mg, 76%, m.p. 175–177 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (br s, 1H), 8.04 (d, J = 5.7 Hz, 1H), 7.20 (d, J = 5.7 Hz, 1H), 6.42 (s, 1H), 1.71 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 150.6, 143.3, 141.8, 140.0, 124.5, 107.4, 95.7, 69.2, 31.0 ppm; IR: ν_{max} 3173, 3140, 2980, 2970, 2805, 2743, 2669, 2551, 1892, 1765, 1615, 1579, 1544, 1441, 1423, 1387, 1371, 1343, 1315, 1248, 1201, 1177, 1149, 1113, 1063, 1007, 981, 964, 944, 929, 869, 842, 823, 810, 761, 689 cm^{-1}; HRMS (ESI) *m*/*z*: calcd. for $C_{10}H_{12}ClN_2O$ $(M + H)^+$ 211.0638, found: 211.0507.

4.1.2.5. General procedure for the synthesis of the library of 4-substituted 2-(1H-pyrrolo[3,2-c]pyridin-2-yl)propan-2-ols via the Suzuki-Miyaura coupling reaction [18].. A 25 mL two necked round bottom flask (the reaction vessel) equipped with a magnetic stirrer bar was charged with 2-(4-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl) propan-2-ol **16** (25.0 mg, 119 μmol, 1.0 equiv), dicyclohexyl(2′,6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (SPhos) (1.23 mg, 2.97 μmol, 0.025 equiv) potassium carbonate (49.2 mg, 356 μmol, 3.0 equiv), palladium(II) acetate (2.66 mg, 11.9 μmol, 0.1 equiv) and potassium organotrifluoroborate (1.5 equiv) and placed under nitrogen. Acetonitrile and water (3/2 v/v), in a separate 50 mL single necked round bottom flask, was degassed with three freeze-pump-thaw cycles. The degassed acetonitrile/water (1.98 mL (1.19 mL + 0.79 mL)) was then added to the reaction vessel via a graduated pipette. The reaction mixture was then heated at 100 °C under nitrogen with magnetically facilitated stirring for the time indicated in Table 1, at which point tlc and GC/MS (EI) analysis showed that the starting material **16** had been consumed. The reaction mixture was cooled and transferred to a separating funnel with the assistance of ethyl acetate (25 mL) and water (25 mL). The mixture was shaken, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 25 mL), with shaking. The organic layers were combined and dried over magnesium sulfate and the solvent was removed *via* rotary evaporation. The residue was purified by flash column chromatography over silica using *n*-hexane/ethyl acetate (99:1 to 0:100) mixtures or *n*-hexane/ethyl acetate (99:1 to 0:100) followed by ethyl acetate/methanol (100:0 to 75:25) mixtures as eluent to give the 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols (**17**–**32**).

*4.1.2.6. 2-(4-phenyl-1H-pyrrolo[3,2-c]pyridin-2-yl)propan-2-ol **(17)**.* Light brown solid, 23.5 mg, 81%, m.p. 108–110 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.66 (br s, 1H), 8.26 (d, J = 5.5 Hz, 1H), 8.07 (d, J = 7.0 Hz, 1H), 7.55–7.35 (m, 3H), 7.32 (d, J = 5.4 Hz, 1H), 6.67 (s, 1H), 1.66 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 151.5, 150.1, 142.0, 141.9, 140.9, 129.5, 129.0, 128.8, 123.6, 106.3, 96.6, 69.3, 31.1 ppm; IR: ν_{max} 3168, 3062, 2978, 2931, 2760, 2561, 2104, 2062, 1737, 1574, 1562, 1546, 1501, 1454, 1417, 1380, 1369, 1309, 1296, 1264, 1238, 1171, 1160, 1141, 1113, 1080, 1059, 1033, 1004, 978, 959, 944, 869, 843, 808, 784, 756, 735, 717, 696 cm^{-1}; HRMS (ESI) *m*/*z*: calcd. for $C_{16}H_{17}N_2O$ $(M + H)^+$ 253.1341, found: 253.1182.

*4.1.2.7. 2-(4-(naphthalen-2-yl)-1H-pyrrolo[3,2-c]pyridin-2-yl) propan-2-ol **(18)**.* Light brown solid, 26.7 mg, 74%, m.p. 124–126 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.69 (br s, 1H), 8.59 (s, 1H), 8.32 (d, J = 5.6 Hz, 1H), 8.28 (dd, J = 8.54, J = 1.73 Hz, 1H), 8.10–7.91 (m, 3H), 7.60–7.48 (m, 2H), 7.37 (d, J = 5.6 Hz, 1H), 6.82 (s, 1H), 1.68 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 151.3, 150.2, 141.9, 141.0, 139.5, 134.4, 134.2, 129.4, 128.53, 128.46, 128.4, 127.7, 127.0, 126.9,

123.8, 106.4, 96.7, 69.3, 31.2 ppm; IR: ν_{max} 3222, 3138, 3051, 2978, 2931, 2853, 2664, 2248, 2238, 2220, 2211, 2196, 2110, 2082, 2048, 1721, 1639, 1607, 1579, 1544, 1510, 1475, 1452, 1421, 1382, 1365, 1294, 1264, 1242, 1235, 1203, 1177, 1162, 1112, 1065, 1046, 1020, 1005, 978, 965, 937, 907, 879, 850, 808, 776, 743, 676 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{20}H_{19}N_2O$ $(M + H)^+$ 303.1497, found: 303.1370.

4.1.2.8. 2-(4-(2-fluoro-[1,1'-biphenyl]-4-yl)-1H-pyrrolo[3,2-c]pyridin-2-yl)propan-2-ol ***(19)***. Light brown solid, 34.0 mg, 83%, m.p. 210–212 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.73 (br s, 1H), 8.30 (d, *J* = 5.5 Hz, 1H), 8.05 (d, *J* = 8.04 Hz, 1H), 8.02–7.90 (m, 1H), 7.77–7.62 (m, 3H), 7.57–7.47 (m, 2H), 7.46–7.36 (m, 2H), 6.78 (s, 1H) 1.69 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 160.6 (d, *J* = 243.9 Hz), 150.7, 149.4, 143.5 (d, *J* = 7.9 Hz), 142.1, 140.9, 136.6, 131.4 (d, *J* = 3.8 Hz), 129.8 (d, *J* = 3.0 Hz), 129.4, 128.6, 125.6 (d, *J* = 3.1 Hz), 123.6, 116.8, 116.5, 106.9, 96.4, 69.3, 31.2 ppm; IR: [20] ν_{max} 3570, 3483, 2976, 2935, 2827, 2110, 2093, 1611, 1581, 1553, 1447, 1428, 1402, 1384, 1318, 1296, 1242, 1205, 1171, 1160, 1136, 1104, 1078, 1061, 1013, 992, 978, 968, 944, 894, 881, 855, 817, 767, 726, 696 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{22}H_{20}FN_2O$ $(M + H)^+$ 347.1560, found: 347.1402.

4.1.2.9. 2-(4-(4-methylphenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl) propan-2-ol ***(20)***. Light brown solid, 22.2 mg, 70%, m.p. 220–220 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.61 (br s, 1H), 8.24 (d, *J* = 5.6 Hz, 1H), 7.97 (d, *J* = 7.4 Hz, 2H), 7.35–7.25 (m, 3H), 6.66 (s, 1H), 2.40 (s, 3H), 1.65 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 151.6, 149.8, 141.8, 140.8, 139.2, 138.4, 129.7, 129.4, 123.4, 106.1, 96.7, 69.2, 31.1, 21.3 ppm; IR: ν_{max} 2974, 2929, 1609, 1581, 1546, 1516, 1460, 1423, 1402, 1380, 1365, 1331, 1315, 1298, 1266, 1171, 1154, 1112, 1063, 1022, 1004, 978, 944, 871, 834, 815, 775, 772, 694, 670, 663 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{19}N_2O$ $(M + H)^+$ 267.1497, found: 267.1362.

4.1.2.10. 2-(4-(3,5-bis(trifluoromethyl)phenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl)propan-2-ol ***(21)***. Light brown solid, 22.7 mg, 49%, m.p. 230–232 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.87 (br s, 1H), 8.67 (s, 2H), 8.36 (d, *J* = 5.6 Hz, 1H), 8.09 (s, 1H), 7.47 (d, *J* = 5.6 Hz, 1H), 6.71 (s, 1H), 1.68 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 151.7, 147.4, 144.3, 142.3, 141.2, 132.2 (q, *J* = 32.9 Hz), 129.4, 124.6 (d, *J* = 270.3 Hz), 123.7, 122.2 (apparent quintet, *J* = 3.6 Hz), 107.7, 95.5, 69.3, 31.1 ppm; [21] IR (cm^{-1}); 3475, 3168, 2978, 2816, 1613, 1581, 1546, 1480, 1460, 1421, 1382, 1369, 1354, 1326, 1305, 1279, 1238, 1169, 1127, 1067, 1005, 992, 953, 935, 905, 881, 849, 832, 823, 804, 775, 719, 707, 678; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{15}F_6N_2O$ $(M + H)^+$ 389.1089, found: 389.0941.

4.1.2.11. 2-(4-(4-(ethylthio)phenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl) propan-2-ol ***(22)***. Light brown solid, 27.3 mg, 73%, m.p. 177–179 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.64 (br s, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 5.6 Hz, 1H), 6.68 (s, 1H), 3.05 (q, *J* = 7.3 Hz, 2H), 1.66 (s, 6H), 1.33 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 150.8, 150.1, 141.9, 140.9, 139.4, 137.8, 129.9, 128.9, 123.4, 106.3, 96.6, 69.3, 31.1, 27.5, 14.7 ppm; IR: ν_{max} 3077, 2974, 2926, 2857, 2766, 2572, 2121, 2099, 1885, 1737, 1609, 1600, 1581, 1562, 1544, 1536, 1510, 1499, 1460, 1445, 1423, 1397, 1382, 1369, 1317, 1298, 1261, 1236, 1186, 1164, 1145, 1112, 1093, 1059, 1018, 979, 961, 940, 869, 842, 825, 808, 780 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{21}N_2OS$ $(M + H)^+$ 313.1375, found: 313.1215.

4.1.2.12. 2-(4-(2-methoxyphenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl) propan-2-ol ***(23)***. Light brown solid, 24.7 mg, 74%, m.p. 108–110 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 8.22 (d, *J* = 5.6 Hz, 1H), 7.55–7.27 (m, 3H), 7.23–6.97 (m, 2H), 6.15 (s, 1H), 3.75 (s, 3H), 1.60 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 158.1, 150.8, 149.3, 141.0, 140.1, 132.2, 130.7, 130.2, 125.7, 121.1, 112.4, 106.3, 97.6, 69.1, 55.6, 31.1 ppm; IR: ν_{max} 3075, 2976, 2935, 2836, 1737, 1667, 1657, 1639, 1603, 1579, 1547, 1562, 1510, 1495, 1467, 1423, 1378, 1298, 1276, 1238, 1181, 1160, 1119, 1102, 1063, 1050, 1024, 976, 942, 873, 845, 827, 810, 795, 760 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{19}N_2O_2$ $(M + H)^+$ 283.1447, found: 283.1731.

4.1.2.13. 2-(4-(4-(tert-butyl)phenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl) propan-2-ol ***(24)***. Light brown solid, 30.5 mg, 83%, m.p. 204–206 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.60 (br s, 1H), 8.25 (d, *J* = 5.1 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 7.7 Hz, 2H), 7.30 (d, *J* = 5.4 Hz, 1H), 6.68 (s, 1H), 1.66 (s, 6H), 1.38 (s, 9H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 151.6, 151.5, 149.9, 141.8, 140.9, 139.2, 129.2, 125.9, 106.1, 96.7, 69.3, 35.2, 31.7, 31.1 ppm; IR: ν_{max} 3224, 3168, 3067, 2965, 2905, 2868, 1609, 1581, 1562, 1544, 1512, 1501, 1460, 1423, 1400, 1380, 1365, 1317, 1296, 1262, 1236, 1177, 1158, 1119, 1063, 1020, 979, 962, 948, 871, 845, 739, 717, 698, 678, 661 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{20}H_{25}N_2O$ $(M + H)^+$ 309.1967, found: 309.1809.

4.1.2.14. 2-(4-(4-fluorophenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl) propan-2-ol ***(25)***. White solid, 26.1 mg, 81%, m.p. 191–193 °C; IR: ν_{max} 3224, 3212, 3159, 2980, 2568, 1739, 1609, 1579, 1562, 1547, 1514, 1460, 1441, 1423, 1400, 1371, 1315, 1298, 1264, 1238, 1223, 1192, 1171, 1158, 1192, 1097, 1091, 1061, 1046, 1018, 979, 961, 944, 871, 842, 775, 724, 696, 661 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d6): δ 10.67 (br s, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 8.18–8.06 (m, 2H), 7.33 (d, *J* = 5.6 Hz, 1H), 7.30–7.20 (m, 2H), 6.67 (s, 1H), 1.66 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 163.6 (d, *J* = 243.6 Hz), 150.3, 150.2, 141.9, 140.9, 138.3 (d, *J* = 3.0 Hz), 131.3 (d, *J* = 8.2 Hz), 123.4, 115.8 (d, *J* = 21.4 Hz), 106.4, 96.4, 69.3, 31.1 ppm; [22] HRMS (ESI) *m/z*: calcd. for $C_{16}H_{16}FN_2O$ $(M + H)^+$ 271.1247, found: 271.1120.

4.1.2.15. 2-(4-(2-(hydroxymethyl)phenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl)propan-2-ol ***(26)***. Light brown solid, 22.0 mg, 66%, m.p. 179–181 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.93 (br s, 1H), 8.30 (d, *J* = 5.8 Hz, 1H), 7.81–7.73 (m, 1H), 7.57–7.50 (m, 1H), 7.50–7.38 (m, 2H), 7.32–7.24 (m, 1H), 6.44 (s, 1H), 4.43 (s, 2H), 1.69 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 152.7, 150.6, 142.5, 141.8, 140.7, 139.4, 131.3, 131.2, 129.2, 128.0, 124.8, 106.8, 96.9, 69.2, 64.8, 31.1 ppm; IR: ν_{max} 3378, 3229, 3205, 3175, 3060, 3030, 2969, 2983, 2942, 2862, 1737, 1721, 1613, 1585, 1572, 1549, 1493, 1458, 1434, 1421, 1398, 1376, 1367, 1350, 1317, 1305, 1292, 1281, 1266, 1240, 1201, 1190, 1177, 1145, 1121, 1104, 1065, 1048, 1002, 964, 946, 883, 871, 851, 806, 780, 754 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{19}N_2O_2$ $(M + H)^+$ 283.1447, found: 283.1642.

4.1.2.16. 2-(4-(cyanophenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl)propan-2-ol ***(27)***. White solid, 16.1 mg, 49%, m.p. 168–170 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.79 (br s, 1H), 8.40–8.25 (m, 3H), 7.95–7.85 (m, 2H), 7.42 (d, *J* = 5.7 Hz, 1H), 6.73 (s, 1H), 1.67 (s, 1H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 151.1, 149.0, 146.2, 142.1, 141.0, 133.0, 130.1, 123.9, 119.5, 112.1, 107.3, 96.2, 69.3, 31.1 ppm; IR: ν_{max} 3226, 3172, 2972, 2929, 2874, 2549, 2227, 1739, 1721, 1678, 1657, 1609, 1579, 1562, 1544, 1510, 1454, 1439, 1423, 1400, 1380, 1371, 1315, 1298, 1262, 1238, 1181, 1158, 1141, 1112, 1065, 1045, 1018, 981, 963, 871, 853, 815, 776, 663 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{16}N_3O$ $(M + H)^+$ 278.1293, found: 278.1153.

4.1.2.17. 1-(4-(2-(2-hydroxypropan-2-yl)-1H-pyrrolo[3,2-c]pyridin-4-yl)phenyl)ethanone ***(28)***. Yellow solid, 30.1 mg, 86%, m.p. 185–187 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.73 (br s, 1H), 8.31 (d, *J* = 5.6 Hz, 1H), 8.22 (d, *J* = 8.3 Hz, 2H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 5.6 Hz, 1H), 6.72 (s, 1H), 2.64 (s, 3H), 1.67 (s, 6H) ppm; ^{13}C

NMR (75 MHz, acetone-d6): δ 197.7, 150.7, 150.0, 146.1, 142.0, 141.0, 137.5, 129.5, 129.1, 123.9, 107.0, 96.4, 69.3, 31.1, 26.8 ppm; IR: ν_{max} 3194, 3132, 3015, 2972, 2929, 2870, 2110, 1736, 1680, 1607, 1579, 1562, 1544, 1510, 1503, 1460, 1439, 1423, 1400, 1382, 1359, 1296, 1268, 1236, 1177, 1154, 1141, 1113, 1065, 1045, 1017, 979, 964, 946, 868, 847, 814, 780, 737, 700, 683 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{18}H_{19}N_2O_2$ $(M + H)^+$ 295.1447, found: 295.1294.

4.1.2.18. Benzyl (4-(2-(2-hydroxypropan-2-yl)-1H-pyrrolo[3,2-c]pyridin-4-yl)phenyl)carbamate ***(29)***. Light brown solid, 40.6 mg, 85%, m.p. 203–205 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.59 (br s, 1H), 8.87 (br s, 1H), 8.24 (d, *J* = 5.6 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.52–7.31 (m, 5H), 7.29 (d, *J* = 5.6 Hz, 1H), 6.71 (s, 1H), 5.21 (s, 2H), 1.66 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 154.4, 151.1, 149.9, 141.9, 140.8, 140.1, 137.9, 136.5, 130.0, 129.3, 128.9, 128.8, 123.3, 118.8, 106.0, 96.8, 69.3, 67.0, 31.1 ppm; IR: ν_{max} 3404, 3246, 3209, 3090, 3071, 3028, 2974, 2939, 2833, 2777, 1702, 1609, 1581, 1544, 1501, 1458, 1425, 1406, 1315, 1298, 1279, 1259, 1236, 1192, 1171, 1141, 1119, 1067, 1020, 1000, 979, 961, 938, 873, 802, 771, 740, 720, 690, 660 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{24}H_{24}N_3O_3$ $(M + H)^+$ 402.1818, found: 402.1675.

4.1.2.19. 2-(4-(4-(trifluoromethyl)phenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl)propan-2-ol ***(30)***. White solid, 27.2 mg, 78%, m.p. 198–200 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.76 (br s, 1H), 8.35–8.25 (m, 3H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 5.5 Hz, 2H), 6.73 (s, 1H), 1.67 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 150.8, 149.6, 145.7, 142.0, 141.0, 130.03 (q, *J* = 31.7 Hz), 129.98, 126.0 (q, *J* = 3.8 Hz), 125.6 (q, *J* = 269.5 Hz), 123,9, 107.1, 96.2, 69.3, 31.1 ppm; [23] IR: ν_{max} 3166, 2976, 2935, 1739, 1615, 1585, 1574, 1547, 1456, 1441, 1425, 1404, 1382, 1324, 1298, 1262, 1238, 1160, 1123, 1110, 1065, 1018, 983, 963, 948, 871, 855, 815, 776, 747, 715, 698, 663 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{16}F_3N_2O$ $(M + H)^+$ 321.1215, found: 321.1058.

4.1.2.20. 2-(4-(methylphenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl) propan-2-ol ***(31)***. Light brown solid, 14.2 mg, 45%, m.p. 173–175 °C; IR: ν_{max} 3132, 3024, 2978, 2864, 2561, 1723, 1607, 1575, 1564, 1544, 1510, 1460, 1413, 1380, 1298, 1264, 1236, 1208, 1160, 1113, 1095, 1061, 1043, 1002, 979, 948, 912, 883, 856, 804, 789, 771, 707 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d6): δ 10.64 (br s, 1H), 8.25 (d, *J* = 5.6 H, 1H), 7.98–7.80 (m, 2H), 7.42–7.18 (m, 3H), 6.66 (s, 1H), 2.43 (s, 3H), 1.65 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 151.7, 149.9, 141.9, 141.8, 140.8, 138.4, 130.1, 129.4, 128.9, 126.6, 123.6, 106.2, 96.7, 69.2, 31.1, 21.6 ppm; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{19}N_2O$ $(M + H)^+$ 267.1497, found: 267.1371.

4.1.2.21. 2-(4-(Thiophen-3-yl)-1H-pyrrolo[3,2-c]pyridin-2-yl) propan-2-ol ***(32)***. Light brown solid, 21.3 mg, 69%, m.p. 125–127 °C; ^{1}H NMR (300 MHz, acetone-d6): δ 10.65 (br s, 1H), 8,20 (d, *J* = 5.6 Hz, 1H), 8,16–8,07 (m, 1H), 7,92 (d, *J* = 4.9 Hz, 1H), 7,57–7,49 (m, 1H), 7,29 (d, *J* = 5.6 Hz, 1H), 6,80 (s, 1H), 1.68 (s, 6H) ppm; ^{13}C NMR (75 MHz, acetone-d6): δ 150.1, 147.1, 144.1, 141.9, 140.5, 129.1, 125.8124.6, 123.1, 106.2, 96.6, 69.3, 31.1 ppm; IR: ν_{max} 3144, 2974, 2931, 2734, 2561, 1737, 1607, 1581, 1562, 1547, 1462, 1423, 1380, 1365, 1283, 1262, 1238, 1177, 1162, 1112, 1048, 979, 955, 897, 877, 860, 842, 804, 782, 763, 737, 689, 672 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{17}H_{19}N_2O$ $(M + H)^+$ 259.0905, found: 259.0778.

4.2. Biological studies

4.2.1. Materials and methods

4.2.1.1. Compounds. The reference compound benznidazole was obtained from Nortec Química (Duque de Caxias, Brazil); the 4-substituted 2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)propan-2-ols **17**–**32** were obtained from Faculdade de Ciências Farmacêuticas - University of São Paulo (São Paulo, Brazil).

4.2.1.2. Cells

4.2.1.2.1. LLC-MK$_2$. The LLC-MK$_2$ cell line was derived from a pooled cell suspension prepared from kidneys removed from Rhesus monkeys. The cells form a contiguous monolayer that can be maintained for several weeks. This cell line was maintained in high glucose DMEM media (Hyclone), supplemented with 10% FBS (Life Technologies), 100 U/ml penicillin (Life Technologies) and 100 μg/mL streptomycin (Life Technologies), henceforth described as "High DMEM Media".

4.2.1.2.2. U2OS. The U2OS cell line was derived from the bone tissue of a 15-year-old human female osteosarcoma patient. U2OS cells exhibit epithelial adherent morphology. This cell line was maintained in High glucose DMEM media, as described above.

4.2.1.2.3. Trypanosoma cruzi Y strain. T. cruzi was donated by A. Avila (Instituto Carlos Chagas, Fiocruz, Curitiba, Brazil). Trypomastigote forms were obtained from the supernatant of LLC-MK$_2$ tissue cultures infected with *Trypanosoma cruzi* Y strain. Infected cultures were maintained in low glucose DMEM media (Vitrocell) supplemented with 2% FBS, 100 U/ml penicillin and 100 μg/mL streptomycin (all from Life Technologies), henceforth described as "Low DMEM Media".

4.2.1.3. Preparation of solutions of compounds. All compounds were dissolved in the proper volume of DMSO to prepare stock solutions in vials; test compounds were diluted at 20 mM. Benznidazole was prepared at 40 mM.

4.2.1.4. Anti-T. cruzi activity assay. The assay was performed as described in Moraes et al. 2014 [23]. Briefly on day one U2OS cells were seeded in black μClear 384-well, tissue culture treated polystyrene (PS) plates (Greiner Bio-One) at in 40 μL of high DMEM media with the aid of a Wellmate Liquid Handler (Thermo-Scientific) and incubated for 24 h at 37 °C/5% CO_2. On day 2, trypomastigotes were harvested from the supernatant of the LLC-MK$_2$ cell cultures that had been infected with *Trypanosoma cruzi* and the trypomastigotes were added to the 384-well microplates (that had been seeded with U2OS cells the previous day as described above) in 10 μL of low-DMEM media/well. On day 3, the test compounds were serially diluted by a factor of 2 (i.e. in 2-fold serial dilutions) in DMSO in a polypropylene 384-well plate (Greiner BioOne) using a 16-channel manual pipette (ThermoScientific). For all tested compounds the highest concentration was 200 μM and the last titration point was 12 nM, and for benznidazole the initial concentration was 400 μM. Test compounds in solution were transferred onto the U2OS/*Trypanosoma cruzi*-containing plates, yielding a final concentration of 1% DMSO and a final volume of 60 μL/well. Non-infected cells and 400 μM-benznidazole-treated wells were used as a positive control, while wells with 1%-DMSO-treated infected cells were used as negative control. Plates were fixed for 15 min with 30 μL/well of 12% paraformaldehyde (the final concentration in the well was 4% paraformaldehyde) 96 h after the addition of the compounds.

4.2.1.5. High content analysis. After fixation, the plates were washed 3 times with PBS and stained with Draq5 (Biostatus), followed by imaging in the High Content Analysis System Operetta (Perkin Elmer) with a 20× objective. The acquired images were analyzed with the High Content Analysis (HCA) software Harmony (Perkin Elmer) for identification, segmentation and quantization of host cell nucleus and cytoplasm and intracellular parasite. The HCA provides as output data for all images from one well the total number of cells, total number of infected cells, total number of intracellular parasites and average number of parasite per infected

cell. Antiparasitic activity data from test compounds was normalized to intraplate controls as described in Moraes et al. 2014 [19]. In this study, EC_{50} was defined as the compound concentration corresponding to 50% normalized activity (inhibition of infection in relation to controls) after 96 h of incubation, and expressed the potency of the compound. The maximum compound activity observed was used to express the compound efficacy. The CC_{50} was defined as the compound concentration that reduces the number of U2OS cells by 50% in relation to infected, non-treated controls. The Selectivity Index (SI) was calculated by dividing the compound CC_{50} value by the EC_{50} value - CC_{50}/EC_{50}). Whenever CC_{50} was not generated through curve fitting, the highest concentration tested (200 μM) was used instead of the CC_{50} value to estimate the SI.

Author contributions

Michael N. Balfour: performing all of the synthetic chemistry and chemical characterization, report writing except for section 2.2 and parts of section 2.3, editing of section 2.2.

Hélio A. Stefani: project development and supervision for the synthetic chemistry side of the project, checking and editing of report.

Caio Haddad Franco and Carolina Borsoi Moraes: biological testing, manuscript writing (section 2.2 and parts of section 2.3) and checking/editing (section 2.2).

Lucio H. Freitas-Junior: contributed reagents, project development and supervision for the biological testing side of the project, manuscript writing (section 2.2 and parts of section 2.3) and checking/editing (section 2.2 and parts of section 2.3).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2017.01.040.

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