Bioorganic & Medicinal Chemistry Letters 23 (2013) 6492–6499

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Dialkylimidazole inhibitors of *Trypanosoma cruzi* sterol 14α-demethylase as anti-Chagas disease agents

Praveen Kumar Suryadevara [a], Kishore Kumar Racherla [a], Srinivas Olepu [a], Neil R. Norcross [a], Hari Babu Tatipaka [a], Jennifer A. Arif [b], Joseph D. Planer [b], Galina I. Lepesheva [d], Christophe L. M. J. Verlinde [c,*], Frederick S. Buckner [b,*], Michael H. Gelb [a,*]

[a] Department of Chemistry, University of Washington, Seattle, WA 98195, USA
[b] Department of Medicine, University of Washington, Seattle, WA 98195, USA
[c] Department of Biochemistry, University of Washington, Seattle, WA 98195, USA
[d] Department of Biochemistry, School of Medicine, Vanderbilt University, Nashville, TN, USA

ARTICLE INFO

Article history:
Received 19 April 2013
Revised 24 July 2013
Accepted 5 August 2013
Available online 12 August 2013

Keywords:
Trypanosoma cruzi
Sterol 14-alpha demethylase
CYP51
Chagas disease
Dialkylimidazole

ABSTRACT

New dialkylimidazole based sterol 14α-demethylase inhibitors were prepared and tested as potential anti-*Trypanosoma cruzi* agents. Previous studies had identified compound **2** as the most potent and selective inhibitor against parasite cultures. In addition, animal studies had demonstrated that compound **2** is highly efficacious in the acute model of the disease. However, compound **2** has a high molecular weight and high hydrophobicity, issues addressed here. Systematic modifications were carried out at four positions on the scaffold and several inhibitors were identified which are highly potent (EC_{50} <1 nM) against *T. cruzi* in culture. The halogenated derivatives **36j**, **36k**, and **36p**, display excellent activity against *T. cruzi* amastigotes, with reduced molecular weight and lipophilicity, and exhibit suitable physicochemical properties for an oral drug candidate.

Chagas disease (American Trypanosomiasis), caused by the protozoan parasite *Trypanosoma cruzi*, is a leading cause of heart failure in Latin America. The disease is endemic throughout much of Mexico, Central and South America, with an estimated 8 million persons infected.[1] Additionally, recent surveys suggest that 300,000 people in the United States, mostly immigrants, have Chagas disease.[2] The disease has an acute and a chronic phase. In the latter the parasite can enter and destroy heart muscle cells, eventually resulting in death due to heart failure. The available drugs, benznidazole and nifurtimox, have debilitating side effects and exhibit low efficacy in the chronic stage of the disease.[3] Hence, better drugs are desperately needed to treat Chagas disease, one of the most neglected tropical diseases.

The antifungal drug posaconazole (**1** in Fig. 1), with an EC_{50} under 1 nM against *T. cruzi* in culture, is currently in clinical trials for Chagas disease, but if effective, high cost will likely limit widespread use.[4] We have previously reported on low-cost dialkylimidazole compounds that kill *T. cruzi* amastigotes in the low nM range.[5] The activity of these compounds is due to inhibition of the enzyme sterol 14α-demethylase[6] (CYP51), essential for the biosynthesis of ergosterol-like sterols, crucial components of the parasite membrane.[7] In the acute mouse model of Chagas disease, several dialkylimidazole compounds reduced parasitemia to microscopically undetectable levels after oral administration.[5,8] However, the compounds are relatively large, hence we attempted to reduce the size of our original lead **2** while maintaining potency to arrive at *T. cruzi* inhibitors like **3** with more drug-like physicochemical properties.

We previously reported a very simple and straightforward synthetic route to arrive at dialkylimidazoles in good yields.[5] Synthesis requires the preparation of two fragments that are then coupled under reductive amination conditions. Analogs **12a–l** were obtained according to Scheme 1. To generate the first fragment, trityl protected imidazole carboxaldehyde **5** was treated with substituted benzylbromides and subsequent deprotection resulted in substituted imidazole carboxaldehyde **6** in moderate to good yields varied depending on substituents on alkyl bromide. The second fragment **11** was derived from **7** using reported methods.[5] Reductive coupling of key intermediates **11** and **6** provided the target compounds **12a–l**.

Preparation of analogs **12r–v** is described in Scheme 2. Phenol derivatives **15** were reacted with alcohols in presence of DIAD and TPP in THF to generate **16** in approximately 45–50% yields.

* Corresponding authors. Tel.: +1 206 543 8865; fax: +1 206 685 1792 (C.L.M.J.V.); tel.: +1 206 598 9148; fax: +1 206 685 8681 (F.S.B.); tel.: +1 206 543 7142; fax: +1 206 685 8665 (M.H.G.).

E-mail addresses: verlinde@ u.washington.edu (C.L.M.J. Verlinde), fbuckner@ u.washington.edu (F.S. Buckner), gelb@chem.washington.edu (M.H. Gelb).

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http://dx.doi.org/10.1016/j.bmcl.2013.08.015

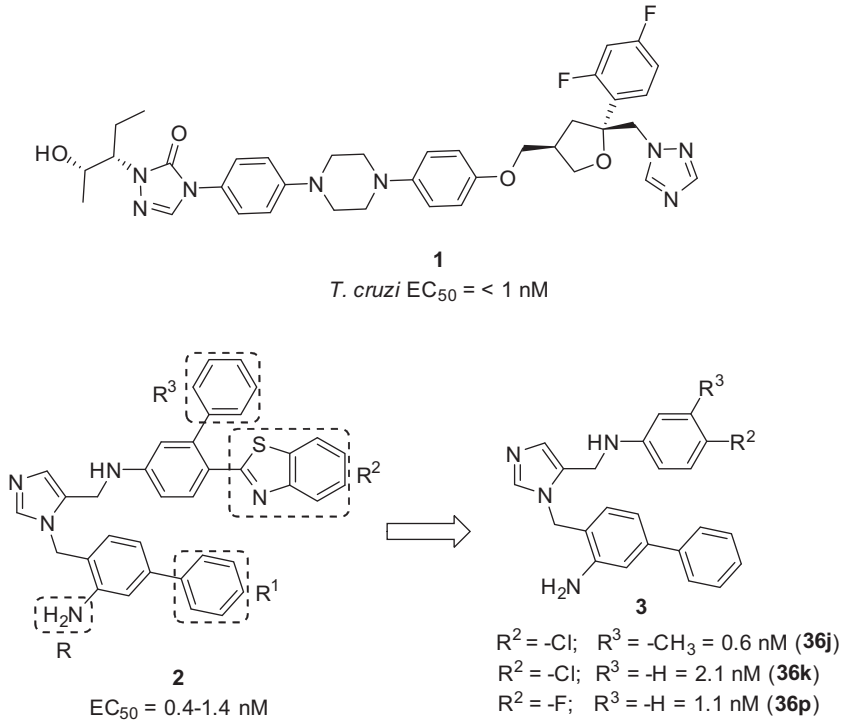
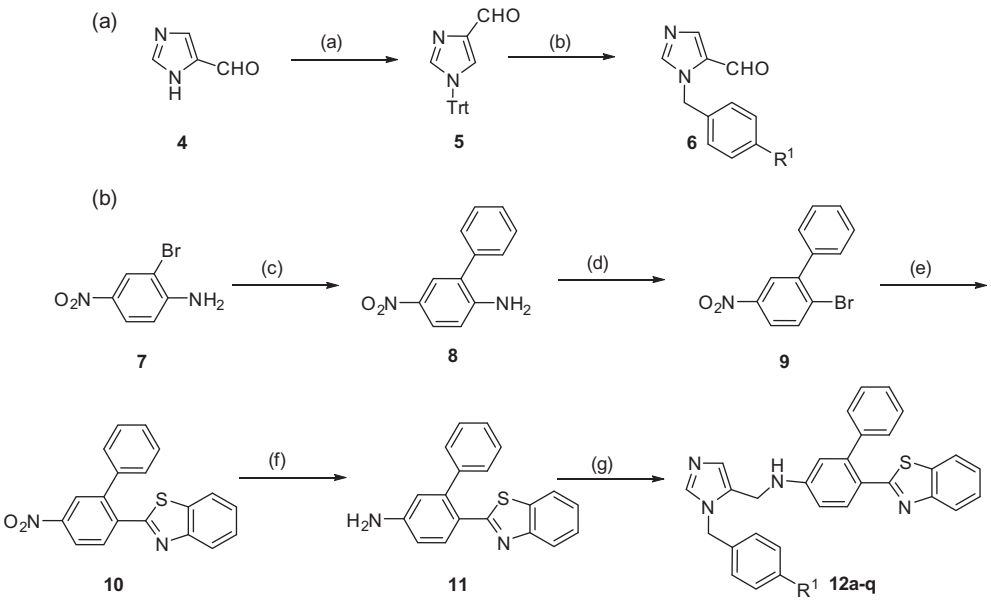


Figure 1. Most potent *T. cruzi* Sterol-14α demethylase inhibitors.

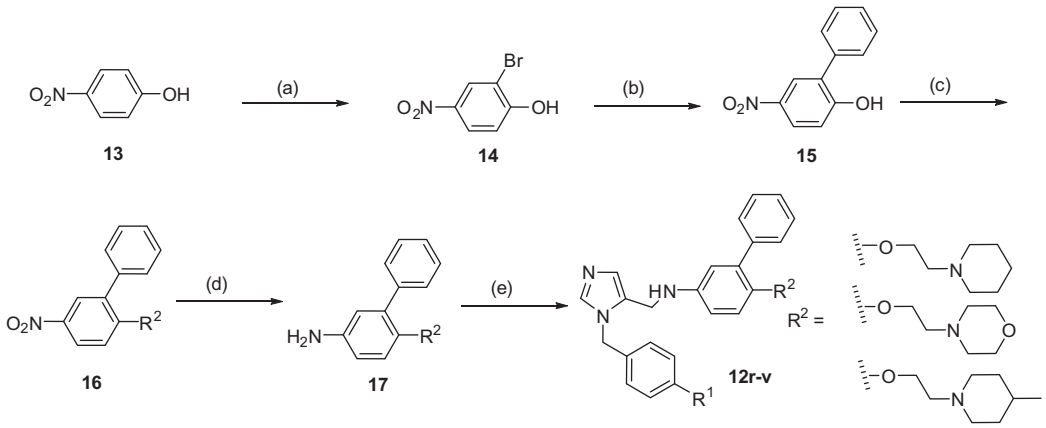


Scheme 1. Reagents and conditions: (a) TrtCl, Et_3N, DMF, rt, 90–94%; (b) $R^1C_6H_4CH_2Br$, CH_3CN, 60 °C, 24 h, 70–75%; (c) $PhRB(OH)_2$, $Ba(OH)_2{\cdot}8H_2O$, $Pd(PPh_3)_4$, DME–H_2O (5:1), reflux, 90%; (d) $NaNO_2$, H_2SO_4, AcOH, $CuBr_2$, HCl, 71%; (e) Benzothiazole, $Pd(PPh_3)_4$, KOAc, DMAC, 160 °C, overnight, 32–35%; (f) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux, 6 h, 76–80%; (g) AcOH, **6**, MeOH, 4 Å mol sieves, $NaBH_3CN$, overnight, rt, 60–65%.

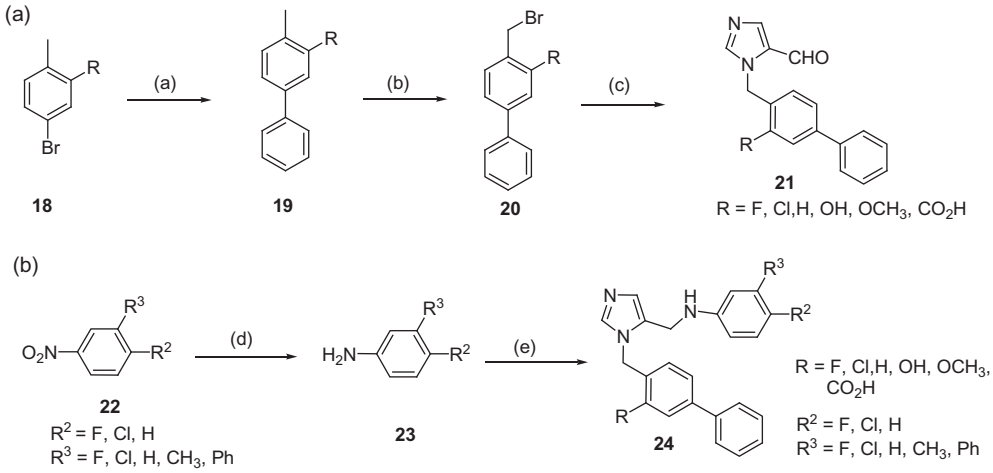
The intermediates were converted to the target compounds using the procedure described in Scheme 1. Synthesis of halogenated dialkylimidazole derivatives is depicted in Schemes 3 and 4. Compound **21** was synthesized as a versatile intermediate for the preparation of several analogs in this study. It was obtained in considerable yield from **18** by Suzuki coupling followed by bromination and further alkylation with **5**.

The second fragment was readily prepared from available nitro derivatives. Fragments were coupled to generate the target compounds **24a–r** in moderate to good yields. Similarly, all amino analogues were prepared as described in Scheme 4.

In our previous studies, inhibitors were potent but large and highly hydrophobic.[6] Hence we decided to produce simplified and more drug-like analogues with reduced molecular weight and lipophilicity (Table 1). We generated new structures by modifying **2** at four positions R, R^1, R^2 and R^3 (Fig. 1). All the synthesized analogs were tested against the clinically relevant amastigote stages of *T. cruzi*.[9]



Scheme 2. Preparation of dialkylimidazoles containing 2-ethoxy-morpholines and piperidines. Reagents and conditions: (a) NBS, FSO_3H, 80%; (b) $PhB(OH)_2$, $Ba(OH)_2{\cdot}8H_20$, $Pd(PPh_3)_4$, DME–H_2O (5:1), reflux, 60%; (c) DIAD, TPP, THF, R^2, 45–50%; (d) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux, 6 h, 76–80%; (e) AcOH, **6**, MeOH, 4 Å mol sieves, $NaBH_3CN$, overnight, rt, 60–65%.



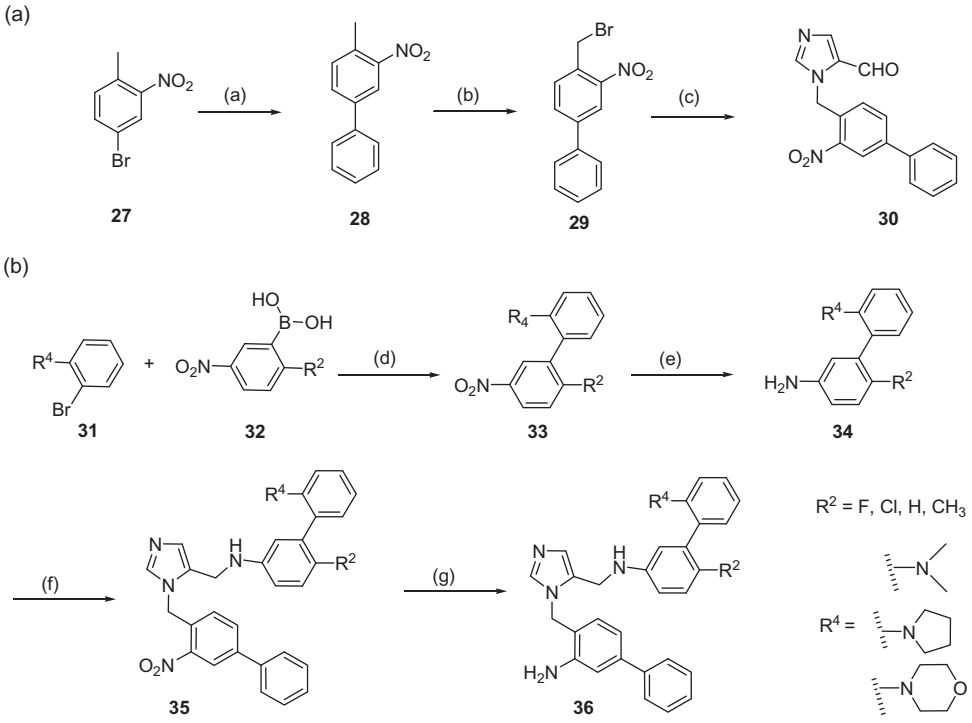
Scheme 3. Preparation of halogenated dialkylimidazoles. Reagents and conditions: (a) $PhB(OH)_2$, $Ba(OH)_2{\cdot}8H_2O$, $Pd(PPh_3)_4$, DME–H_2O (5:1), reflux, 90%; (b) NBS, CCl_4, benzoyl peroxide, reflux, 85%; (c) **5**, CH_3CN, 60 °C, 24 h, 70–75%; (d) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux, 6 h, 76–80%; (e) AcOH, **21**, MeOH, 4 Å mol sieves, $NaBH_3CN$, overnight, rt, 60–65%.

Initial modifications at R^1 in compound **12** replaced the phenyl group with various heterocycles like furan, pyridine and thiophene (**12a**–**c**), which consequently, did little to modulate activity against *T. cruzi*. However, introduction of polar functionality at the 2-position on R^1 or lipophilic groups at the 4-position on R^1 (**12d**–**g**) was less well tolerated.

We next investigated the effect of substitution on the R^3 phenyl system. Introduction of polar functional groups at the *para* position on the terminal phenyl (R^3) such as hydroxy and methoxy had little effect on potency. However, the introduction of an amino group at the 4-position on R^3 (**12k**) dramatically inhibited the *T. cruzi* cultures at low nanomolar level with >10-fold increase in potency (EC_{50} = 1.6 nM) compared with compound **12**.

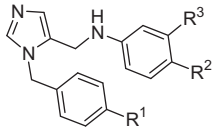
Previously explored SAR of the benzothiazole moiety[6] suggested that benzothiazole is at the periphery of the active site, partially exposed to solvent. Replacing it by a simple chloro retains the potency against *T. cruzi* and, importantly, reduces the molecular mass by 100.[6] By retaining –Cl at R^2 position, we obtained an extra molecular mass window within Lipinski space to explore R^3 with a variety of heterocyclic as well as saturated heterocyclic systems (**12n**–**q**). However, associated modifications did not improve potency. In addition, replacement of the benzothiazole moiety at R^2 with alkoxy and alkylamino linked heterocycles, (**12r**–**v**), displayed as much as a 10-fold drop in potency. These analogues suggest a limited tolerance at R^3 for further modifications containing large, flexible linked heterocycles.

Considering the dialkyl imidazole core, we began to focus our attention on smaller functional groups at the R^2 and R^3 positions, to try to further improve physicochemical properties, whilst improving or at least, retaining potency against *T. cruzi* amastigotes (Table 2). Furthermore, we investigated the importance of the –NH_2 group on the biphenyl rings of the imidazole subunit, for activity against *T. cruzi*. Two of the most potent compounds from previous studies[6] both comprise an amino functionality at the C-2 position of the biphenyl attached to the imidazole. The introduction of the C-2 amino functionality to compound **12** to afford compound **2** resulted in a 20-fold increase in potency. The development of an in-house homology model of *T. cruzi* CYP51, using the previously published *Mycobacterium tuberculosis* crystal structure,[10] has shown that this remarkable increase in activity can be attributed to a key H-bond interaction of the aniline moiety with a histidine residue in the active site of *T. cruzi* CYP51. However, replacement of the aniline moiety with other functional groups such as –OMe (**24n**), –OH (**24o**) and –COOH (**24q**), led to a >27-fold drop in potency, highlighting the importance of this key amino/histidine interaction. Compounds such as **24a** and **24o**, without the aniline moiety, also exhibited sub-20 nM activity against *T. cruzi*. Interestingly, compound **24a** demonstrated that



Scheme 4. Synthetic strategy for dialkylimidazole analogs bearing $-NH_2$ at R. Reagents and conditions: (a) PhB $(OH)_2$, $Ba(OH)_2{\cdot}8H_2O$, $Pd(PPh_3)_4$, DME–H_2O (5:1), reflux, 90%; (b) NBS, CCl_4, benzoyl peroxide, reflux, 85%; (c) **5**, CH_3CN, 60 °C, 24 h, 70–75%; (d) $Ba(OH)_2{\cdot}8H_2O$, $Pd(PPh_3)_4$, DME–H_2O (5:1), reflux, 90%; (e) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux, 6 h, 76–80%; (f) AcOH, **30**, MeOH, 4 Å mol sieves, $NaBH_3CN$, overnight, rt, 60–65%; (g) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux, 5–7 h, 75–82%.

Table 1
Activity of dialkylimidazoles with variations at R^1, R^2 and R^3 against *T. cruzi* amastigotes

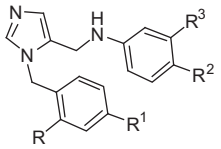


12a-v

Compd No.	MWT	log*P*	PSA (Å^2)	R^1	R^2	R^3	*T. cruzi* EC_{50} (nM)
12	548	8.4	42.7	Phenyl	Benz[b]	Phenyl	20.0
12a	539	7.4	55.9	2-Furan	Benz	Phenyl	21.2
12b	550	7.5	55.6	2-Pyridine	Benz	Phenyl	19.3
12c	555	8.2	42.7	2-Thiophene	Benz	Phenyl	11.1
12d	564	7.6	68.8	2-NH_2-Ph	Benz	Phenyl	75.4
12e	565	8.1	63.0	2-OH-Ph	Benz	Phenyl	123.2
12f	563	8.9	42.7	4-Me-Ph	Benz	Phenyl	50.0
12g	583	9.0	42.7	4-Cl-Ph	Benz	Phenyl	48.5
12h	563	8.9	42.7	3-Me-Ph	Benz	Phenyl	5.4
12i	565	8.1	63.0	Ph	Benz	4-OH-Ph	11.0 (20,010)[a]
12j	579	8.2	52.0	Ph	Benz	4-OMe-Ph	10.0
12k	564	7.6	68.8	Ph	Benz	4-NH_2-Ph	1.6 (27,500)[a]
12l	574	8.2	66.5	Ph	Benz	4-CN-Ph	32.0
12m	466	7.0	29.9	Ph	Methyl	2,6-Di-F-Ph	36.6
12n	451	5.6	42.7	Ph	Chloro	4-Pyridine	27.2
12o	439	5.6	34.8	Ph	Chloro	Pyrrole	30.4
12p	457	6.1	33.1	Ph	Chloro	Piperidine	53.6
12q	451	5.6	42.7	Ph	Chloro	3-Pyridine	64.8
12r	545	5.9	51.6	Ph	$-O(CH_2)_2$-Mor[c]	Phenyl	35.2
12s	544	5.9	54.4	Ph	$-NH(CH_2)_2$-Mor	Phenyl	115.2
12t	543	6.9	42.3	Ph	$-O(CH_2)_2$-Pip[d]	Phenyl	316.8
12u	542	6.6	45.1	Ph	$-NH(CH_2)_2$- Pip	Phenyl	194.0 (10,700)[a]
12v	558	5.9	45.6	Ph	$-O(CH_2)_2$-4-Me-Pip	Phenyl	97.4 (4,470)[a]

[a] Host cell activity against CRL-8155 IC_{50} (nM).
[b] Benzothiazole.
[c] Morpholine.
[d] Piperidine.

Table 2
Activity of halogenated dialkylimidazoles against *T. cruzi* amastigotes



24a-r

Compd No.	MWT	log*P*	PSA (Å^2)	R	R^1	R^2	R^3	*T. cruzi* EC$_{50}$ (nM)
12	548	8.4	42.7	H	Phenyl	Benz[b]	Phenyl	20.0
2	564	7.6	68.8	NH_2	Phenyl	Benz	Phenyl	1.0
24a	451	6.5	29.9	F	Phenyl	F	Phenyl	12.0
24b	375	4.8	29.9	F	Phenyl	F	H	70.2
24c	380	5.3	29.9	F	Phenyl	F	Methyl	53.0
24d	409	5.4	29.9	F	Phenyl	F	Cl	49.0
24e	393	5.0	29.9	F	Phenyl	F	F	46.0
24f	331	3.8	29.9	F	Fluoro	F	Methyl	272.0
24g	335	3.5	29.9	F	Fluoro	F	F	212.0
24h	317	3.3	29.9	F	Fluoro	F	H	354.0
24i	408	5.7	29.9	Cl	Phenyl	–Cl	H	83.2
24j	405	5.8	29.9	Cl	Phenyl	F	Methyl	26.0
24k	426	5.9	29.9	Cl	Phenyl	F	Cl	48.7
24l	409	5.4	29.9	Cl	Phenyl	F	F	38.1
24m	469	6.6	29.9	H	Phenyl	F	2,6-di-F-Phe	11.7 (17,460)[a]
24n	480	6.6	39.1	OCH_3	Phenyl	Cl	Phenyl	35.1
24o	465	6.5	50.1	OH	Phenyl	Cl	Phenyl	5.9 (21,500)
24p	564	8.0	63.0	OH	Phenyl	Benz[b]	Phenyl	89.3
24q	592	7.2	80.0	CO_2H	Phenyl	Benz	Phenyl	>1000
24r	579	8.2	52.0	OCH_3	Phenyl	Benz	Phenyl	27.2

[a] Host cell activity against CRL-8155 IC$_{50}$ (nM).
[b] Benzothiazole.

the benzothiazole moiety at the R^2 position could be replaced with only an F atom, albeit with the aniline moiety also replaced with an F atom. However, the changes highlighted by compound **24a** compared with compound **12**, showed that small, lipophilic groups at R^2 were well tolerated, thus reducing molecular weight and log*P* whilst retaining activity. In addition, desirable levels of potency could be attained by the introduction of a combination of halogen atoms at R, R^1, R^2 and R^3, whilst still retaining sub-100 nM levels of potency against *T. cruzi*.

Also worthy of note is compound **24b** in which the phenyl at R^3 was replaced with hydrogen, resulting in less than fourfold drop in potency compared with compound **12**, against *T. cruzi*, supporting the fact that smaller lipophilic groups were well tolerated at R^2 and R^3.

With this information in hand, a small set of chlorinated analogs (**24i**–**l**) were designed and tested against *T. cruzi* cultures. The comparable potencies of analogues **24a**–**l** suggest that all of these analogues adopt similar binding conformations. In addition, a combination of fluorine and chlorine atoms at R^1, R^2 and R^3 could be utilized to reduce molecular weight and log*P*, thus improving physicochemical properties, whilst retaining activity against *T. cruzi*.

We also examined other aromatic substituents to replace the aniline moiety (**24n**–**r)** as described in Table 2. Compound **24o** showed considerable improvements in potency (EC$_{50}$ of 5.9 nM) compared with the compounds in the same series, which lack the amino group on the biphenyl imidazole subunit, suggesting that replacement of the amino group with alternative small, hydrogen bond donors, may be tolerated. However, the larger polar –COOH group (**24q**) was not tolerated. These studies suggest some flexibility in the functionality placed at the R position, with a preference for small H-bond donor groups.

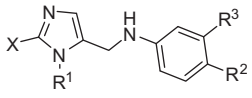
Alternative functional groups were also investigated to try to optimize the potency against *T. cruzi* (Table 3). Methylation at C-2 position of the imidazole (**25a**–**d**) did not show activity even at 1 μM. The idea was to prevent the binding of the imidazole to human CYP's but this series was discarded due to dramatic loss in potency, highlighting the importance of the imidazole–nitrogen binding interaction to the heme moiety in the *T. cruzi* CYP51 active site for activity. Replacement of the biphenyl on the imidazole by ethyl piperidines and indole derivatives (**25e**–**h**) was not tolerated. These results also demonstrate the critical requirement of the biphenyl system attached to the imidazole subunit. However, potent analogues were also observed when the central phenyl ring was replaced with pyridine. Replacement of pyridine and keeping the biphenyl moiety on the imidazole (**26b**) showed activity at 12.5 nM against *T. cruzi* and further addition of an amino group on biphenylimidazole (**26c**) led to an EC$_{50}$ of 0.2 nM. Inhibition of the proposed biological target by the dialkylimidazole series was confirmed by spectrophotometric studies. Using recombinant *T. cruzi* sterol 14α-demethylase, we have previously shown that **26c** binds to the haem moiety in the CYP51 active site as characterized by a Soret Type II binding spectra (Fig. 2).[6]

Utilizing compound **26c** as a reference point for further synthetic modifications, we initially replaced the methoxy at R^2 with the metabolically more stable fluorine group (**36n**) to evaluate the effects of further modifications at R^3. Modifications at R^3 with the larger chlorine atom at the R^2 position were also investigated (Table 4).

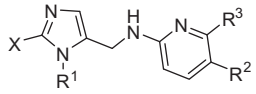
Modification of the phenyl ring at R^3 with saturated ring systems was poorly tolerated. However, direct replacement of the phenyl ring at R^3 with –Cl (**36f**), imidazole (**36h**) and pyrrole (**36i**), also displayed sub10 nM levels of potency against *T. cruzi*.

The most potent analogues against *T. cruzi* were observed when the phenyl at R^3 was replaced with minimalistic groups such as –CH_3 (**36j**) and –H (**36k**). In addition, both examples indicate that the size of groups at R^3 can be significantly reduced, while still retaining activity against *T. cruzi* amastigotes. Furthermore, similar observations were made in the case of fluorinated analogs. It is well known that incorporation of fluorine into a drug allows simultaneous modulation of electronic, lipophilic and steric parameters

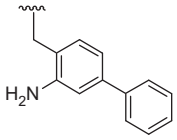
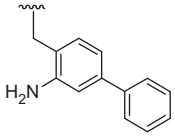
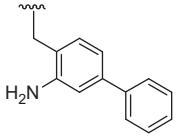
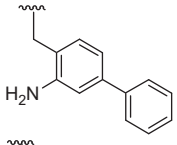
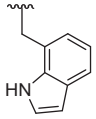
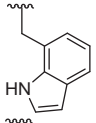
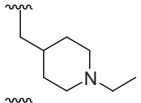
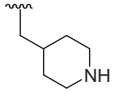
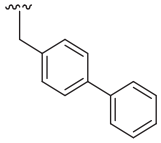
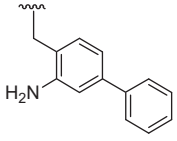
Table 3
Activity of dialkylimidazoles varied at X, R^1, R^2 and R^3 positions and Pyridine based dialkylimidazoles against *T. cruzi*



25a-h



26a-c

Compd No.	MWT	log*P*	PSA (Å^2)	x	R^1	R^2	R^3	*T. cruzi* EC_{50} (nM)
25a	404	4.1	55.8	Me		F	F	>1000
25b	400	4.5	55.8	Me		F	Me	>1000
25c	420	4.6	55.8	Me		F	Cl	>1000
25d	386	4	55.8	Me		F	H	>1000
25e	396	4.8	45.6	H		F	Phenyl	333.0
25f	412	5.2	45.6	H		Cl	Phenyl	333.0
25g	408	4.3	33	H		Cl	Phenyl	>1000 (17,400)[a]
25h	380	3.5	41.8	H		Cl	Phenyl	>1000
26a	370	4.2	52	H		OMe	Phenyl	686.1
26b	446	5.8	52	H		OMe	Phenyl	12.5
26c	461	5.0	78	H		OMe	Phenyl	0.2 (>5000)[a]

[a] Host cell activity against CRL-8155 IC_{50} (nM).

all of which can critically influence the pharmacokinetic properties of drugs.[11] In this context several fluorinated dialkylimidazole based sterol 14α-demethylase inhibitors were synthesized and evaluated. All the synthesized fluoro analogues showed excellent potency against *T. cruzi*. Remarkably, compound **36p**, in which R^3 phenyl group was removed completely, still exhibited high potency of 1.1 nM.

As can be seen in Table 4, the majority of analogues prepared were found to be extremely active with EC_{50} values of <1 nM. This is a considerable improvement in potency in this series leading to

anti-*T. cruzi* activity comparable to that of posaconazole (**1**). The current SAR study clearly shows that 2-amino biphenyl as R-R^1 system is superior for potency and also that halogens (–F, –Cl) are well tolerated at the R^2 position.

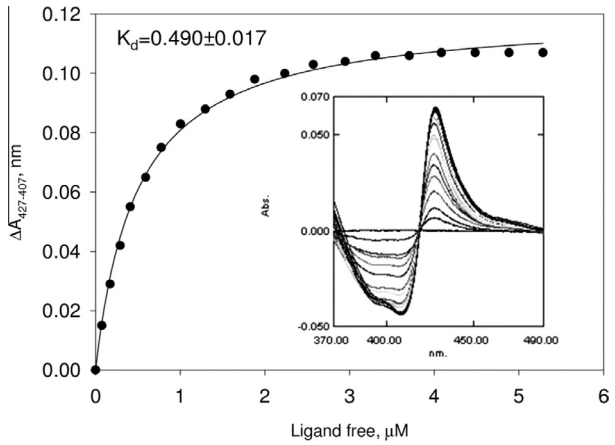


Figure 2. Spectral response of *T. cruzi* CYP51 to **26c**. Titration curve and difference binding spectra (inset). P450 concentration was 2.2 μM; **26c** titration range 0.4–7.6 μM (titration steps of 0.4 μM). Methods as described previously.[6].

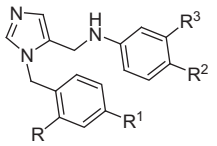
Twelve of the more potent compounds in this series were tested for cytotoxicity to the mammalian lymphocytic cell line CRL-8155. This is a relatively sensitive cell line to the cytotoxic effects of chemicals.[12] The tested dialkylimidazoles were only cytotoxic at relatively high concentrations in the range of 5–10 μM demonstrating a selectivity margin over *T. cruzi* amastigotes of >10,000-fold in many cases.

Overall in this study we synthesized 75 dialkylimidazole-based inhibitors of sterol-14α-demethylase and evaluated them against *T. cruzi*, the causative agent of Chagas disease. We previously reported that, dialkylimidazole based inhibitors are well tolerated in animals infected with acute stage of the disease. These new analogues are structurally simple, display suitable physicochemical properties for that of an oral drug candidate and can be efficiently synthesized at low-cost. In addition, novel compounds reported herein display excellent potency against *T. cruzi* amastigotes with activity comparable to posaconazole and show potential as novel therapeutics for the treatment of Chagas disease.

Acknowledgments

Mammalian cell cytotoxicity experiments were assisted by Nicole A. Duster. This work was supported by grants from the National Institutes of Health (NIH) AI070218, AI054384, and GM067871. We appreciatively acknowledge the financial support

Table 4
In vitro anti-*T. cruzi* activities of highly potent dialkylimidazole analogs bearing –NH$_2$ at R (Scheme 4)



36a-x

Compd No.	MWT	log*P*	PSA (Å^2)	R	R^1	R^2	R^3	*T. cruzi* EC$_{50}$ (nM)
26c	461	5.0	78	NH$_2$	Phenyl	OMe	Phenyl	0.2
36a	534	6.5	59.1	NH$_2$	Phenyl	Cl	2-Pyrro[e]-phe	87.0
36b	550	5.9	68.3	NH$_2$	Phenyl	Cl	2-Mor-phe	24.5
36c	449	4.7	68.7	NH$_2$	Phenyl	Cl	2-Pip-phe	20.8
36d	508	6.1	59.1	NH$_2$	Phenyl	Cl	2-N,N-Di-Me-Phe	19.0
36e	480	5.1	81.8	NH$_2$	Phenyl	Cl	4-NH$_2$-Phe	0.3 (12,900)[a]
36f	423	5	55.8	NH$_2$	Phenyl	Cl	Cl	9.0
36g	472	5.3	59.1	NH$_2$	Phenyl	Cl	Pip[d]	1.1 (>5000)[a]
36h	454	3.5	73.7	NH$_2$	Phenyl	Cl	Imidazole	5.0 (14,600)[a]
36i	453	4.8	60.8	NH$_2$	Phenyl	Cl	Pyrrole	3.8
36j	386	4.4	55.8	NH$_2$	Phenyl	Cl	Methyl	0.6 (12,900)[a]
36k	388	4.3	55.8	NH$_2$	Phenyl	Cl	H	2.1
36l	484	5.8	55.8	NH$_2$	Phenyl	–F	2,6-di-F -Phe	0.4
36m	388	4.3	55.8	NH$_2$	Phenyl	F	Cl	1.2
36n	448	5.5	55.8	NH$_2$	Phenyl	F	Phenyl	0.8 (18,800)[a]
36o	390	4	55.8	NH$_2$	Phenyl	F	F	3.2
36p	372	3.8	55.8	NH$_2$	Phenyl	F	H	1.1
36q	480	6.2	55.8	NH$_2$	Phenyl	Methyl	2,6-di-F-Phe	0.4 (>5000)[a]
36r	ND	ND	ND	NH$_2$	Phenyl	O(CH$_2$)$_2$-mor[b]	4-Cl-Phe	1.5
36s	572	5.1	71.5	NH$_2$	2-Pyridine	O(CH$_2$)$_2$-4-Me pip[c]	Phenyl	5.8 (5270)[a]
36t	ND	ND	ND	NH$_2$	Cl	Benz[d]	Phenyl	1.4
36u	449	4.7	68.7	NH$_2$	Methoxy	F	Phenyl	14.5
36v	406	4.5	55.8	NH$_2$	Cl	F	Phenyl	12.8
36w	372	3.8	55.8	NH$_2$	H	F	Phenyl	232.6
36x	399	2.2	68.3	NH$_2$	Morpholine	F	F	358.0

[a] Host cell activity against CRL-8155 IC$_{50}$ (nM).
[b] Benzothiazole.
[c] Morpholine.
[d] Piperidine.
[e] Pyrrolidine.

for this project from Drugs for Neglected Diseases Initiative (DNDi). For the work described in this paper, DND*i* allocated non-earmarked funding (Department for International Development (DFID)/United Kingdom, Spanish Agency for International Development Cooperation (AECID)/Spain, Médecins Sans Frontières (Doctors without Borders)/International). The donors had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.08.015.

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