Journal of Medicinal Chemistry

BRIEF ARTICLE

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Novel Lipophilic Acetohydroxamic Acid Derivatives Based on Conformationally Constrained Spiro Carbocyclic 2,6-Diketopiperazine Scaffolds with Potent Trypanocidal Activity

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Supporting Information

ABSTRACT: We describe novel acetohydroxamic acid derivatives with potent activity against cultured bloodstream-form *Trypanosoma brucei* and selectivity indices of >1000. These analogues were derived from conformationally constrained, lipophilic, spiro carbocyclic 2,6-diketopiperazine (2,6-DKP) scaffolds by attaching acetohydroxamic acid moieties to the imidic nitrogen. Optimal activity was achieved by placing benzyl groups adjacent to the basic nitrogen of the 2,6-DKP core. *S*-Enantiomer **7d** was the most active derivative against *T. brucei* (IC_{50} = 6.8 nM) and *T. cruzi* (IC_{50} = 0.21 μM).

INTRODUCTION

Human African trypanosomiasis is caused by tsetse fly transmitted parasites of the *Trypanosoma brucei* species complex. Over 50 million people in sub-Saharan Africa are at risk.[1a,b] In 2009, there were 30 000 cases,[1c] although during epidemics, this level can increase >10-fold.[1d] Chagas disease (or American trypanosomiasis) is caused by *Trypanosoma cruzi* and affects 8−10 million people in Latin America, resulting in >15 000 deaths per year.[1a,b,2] Therapy for trypanosomal infections is unsatisfactory because of toxic side effects, the development of resistance, and in many cases the need for parenteral administration.[3] With no immediate prospect of vaccines, there is a great need to develop new antitrypanosome agents with an acceptable efficacy and safety profile.

Amantadine and rimantadine are anti-influenza A drugs that inhibit virus replication at micromolar concentrations.[4] Bloodstream-form *T. brucei* are sensitive in vitro to amantadine and rimantadine, particularly the latter drug (IC_{50} = 7 μM).[5] Rimantadine also has activity against the trypanosomatid parasites *T. cruzi* and *Leishmania major*.[5] It was subsequently reported that a series of aminoadamantane and aminoalkylcyclohexane derivatives were effective in inhibiting growth of *T. brucei* in vitro and in vivo and that inhibition was correlated with lipophilicity. Some of these derivatives showed submicromolar trypanocidal activities,[6] the most potent being **1** and **2** (Figure 1). Recently, we described the synthesis and trypanocidal properties of several nitrogen-containing adamantane derivatives.[7,8] Of these, **3**−**5** (Figure 1) were active in vitro against *T. brucei*. Oxazolone **3**[8] was the most active, with a potency that was 3-fold higher than rimantadine and at least 45-fold greater than amantadine.

To determine how structural features affect the trypanocidal activity of compounds based on adamantane or other lipophilic carbocycles, we explored spiro 2,6-diketopiperazine derivatives **6a** and **6b** (Figure 1) (synthesis of **6a** has been described by us previously[9]). A preliminary screen of 2,6-diketopiperazines (2,6-DKPs) **6a** and **6b** (5 μg mL^{-1}) against bloodstream-form

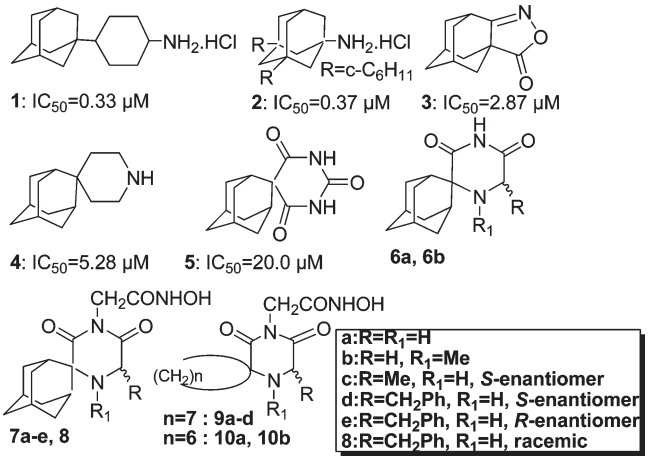


Figure 1. Structures of lipophilic adamantane aminoderivatives **1**−**5**[5−8] with activity against *T. brucei*, and structures of the 2,6-DKPs **6a** and **6b** and the new hydroxamic acid derivatives **7a**−**e**, **8**, **9a**−**d**, **10a**, and **10b**.

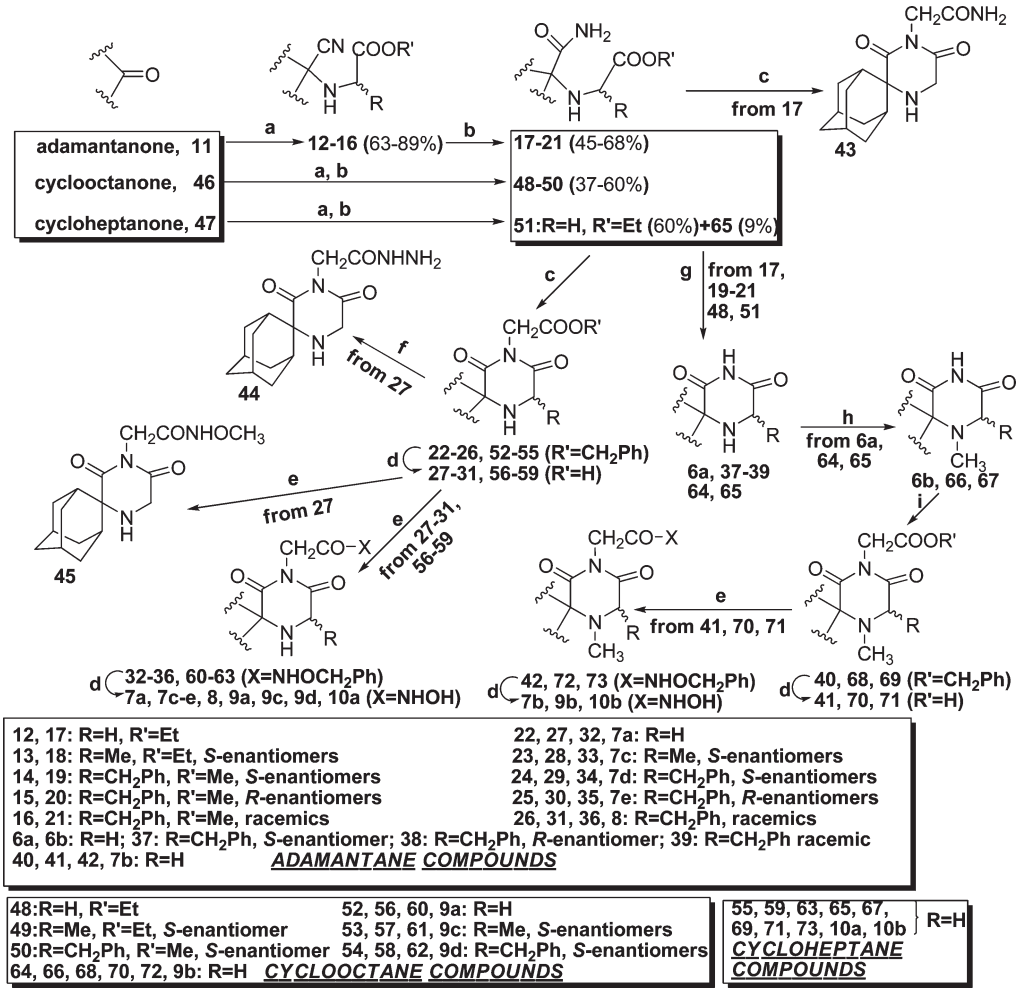
T. brucei revealed that 2,6-DKP **6a** was inactive while its *N*-4 methyl counterpart **6b** had only marginal effects on parasite growth (40% inhibition). Despite these results, we have continued to investigate the lipophilic spiro carbocyclic 2,6-DKP core with the view of improving antitrypanosome potency.

Several essential trypanosomatid metalloenzymes have been identified, and their inhibition has been recognized as an approach to chemotherapy.[10−17] The focus has been zinc or iron metalloenzymes.[11−15,17]

Hydroxamic acids form strong complexes with a range of metals, especially iron.[18] This has been exploited to produce inhibitors of metalloenzymes implicated in the pathophysiology

Received: February 25, 2011
Published: May 04, 2011

Scheme 1[a]



[a] Reagents and conditions: (a) NaCN, appropriate α-amino acid alkyl ester hydrochloride, DMSO/H_2O 29:1 (v/v), room temp, 48 h; (b) (i) H_2SO_4 97%, room temp, 24 h for **17**, **18**, **48** or H_2SO_4 97%, CH_2Cl_2, room temp, 48 h for **19**−**21** or 24 h for **49**−**51**; (ii) ice and then aq NH_3 26% to pH 7−8; (c) (i) $(Me_3Si)_2NK$ (1 equiv), THF, 0−5 °C, then room temp, 1 h, argon; (ii) $BrCH_2CO_2CH_2Ph$ or $BrCH_2CONH_2$ only for **43**, DMF, room temp, 48 h, argon, 78−94% for **22**−**26**, **52**−**54**, 62% for **55** from **47**, 50% for **43**; (d) H_2/Pd 10%, EtOH for **27**, **28**, **41**, **56**, **57**, **59**, **70**, **71**, **7a**−**e**, **8**, **9a**−**d**, **10a**, **10b** or EtOH/AcOEt 3:2 (v/v) for **29**−**31**, **58**, 50 psi, room temp, 3 h, >99% for **27**−**31**, **56**−**59**, **41**, **70**, **71**, 80−95% for **7a**−**e**, **8**, **9a**−**d**, **10a**, **10b**; (e) (i) CDI, THF for **32**−**36**, **42**, **45**, **61**, **62**, **72**, **73** or THF/DMF 3:4 for **60** or THF/DMF 4:1 for **63**, 28 °C, 1 h, argon; (ii) $PhCH_2ONH_2 \cdot HCl$ or $CH_3ONH_2 \cdot HCl$ only for **45**, Et_3N, 28 °C, 25 h, argon for **33**−**35**, **61**, **62**, or 28 °C, 24 h, then 45 °C, 1 h, argon for **32**, **36**, **42**, **45**, **60**, **63**, **72**, **73**, 63−95%; (f) as (e) using $H_2NNHCO_2CH_2Ph$, THF, 28 °C, 25 h, then as (d), EtOH, 76%; (g) as (c) (i), then CF_3CO_2H (1 equiv), >99%; (h) (i) aq CH_2O 37%, MeOH/THF 1:1 for **6b** or MeOH/THF 1:3 for **66**, **67**, room temp, 3 h, then $NaCNBH_3$, room temp, 4 h at pH 6−7 (maintained by adding AcOH); (ii) 1N NaOH and Na_2CO_3 to pH 8, 80−92%; (i) NaH, DMF, room temp, 1 h, argon and then as (c) (ii) using $BrCH_2CO_2CH_2Ph$, 83−95%.

of human diseases[19−21] (cancer, inflammatory conditions, etc). Of particular interest are the zinc and iron metalloenzyme hydroxamate inhibitors and their use as matrix metalloproteinase (MMP), histone deacetylase (HDAC), and 5-lipoxygenase (5-LO) inhibitors.[19−21] In all of the above cases, the hydroxamic acid moiety is required for inhibition, which is mediated by binding to the metal ion in the catalytic site.

Studies on the trypanocidal activity of hydroxamic acid-based derivatives have been limited. Hydroxamate analogues are selective inhibitors of *T. brucei* 6-phosphoglyconate dehydrogenase (*Tb*6PGDH). They have a sugar-like backbone (hydroxamate derivatives of 4-phospho-D-erythronic acid) and mimic the high-energy intermediates of the 6PGDH enzymatic reaction.[22] Despite their potency and selectivity, these analogues were devoid of significant in vitro activity. Another compound of interest is the alternative oxidase inhibitor salicylhydroxamic acid, which has some trypanocidal activity, although this may be due to the hydroxyl substituted benzoic acid moiety.[23]

In this current study, we used lipophilic 2,6-DKPs **6a** and **6b** as conformationally constrained scaffold molecules onto which we attached hydroxamate units as potential metal-chelating moieties. We describe the synthesis of several derivatives (Figure 1) that have potent trypanocidal activity while being relatively nontoxic to mammalian cells.

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As depicted in Scheme 1, carboxylic acids **27**−**31**, **41**, **56**−**59**, **70**, and **71** were the key structures in preparing the new target compounds. Thus, their coupling with *O*-benzylhydroxylamine in

dx.doi.org/10.1021/jm200217m |*J. Med. Chem.* 2011, 54, 5250–5254

Table 1. Activity of Acetohydroxamic Acid Analogues 7a−e, 8, 9a−d, 10a, and 10b (Figure 1) Tested against Cultured Bloodstream-Form *T. brucei* (pH 7.4) and *T. cruzi* Epimastigotes and Cytotoxicity of the Most Active Compounds against Cultured Rat Skeletal Myoblast L6 Cells (Supporting Information)

	activity					
	T. brucei		*T. cruzi*		cytotoxicity	
compd	IC_{50} (nM)[a,b]	IC_{90} (nM)[a,b]	IC_{50} (μM)[a]	IC_{90} (μM)[a]	IC_{50} (μM)[c]	SI[d]
7a	90 ± 16 (79 ± 6)	155 ± 7 (148 ± 8)	5.51 ± 0.68	11.11 ± 1.19	>325	>3600
7b	193 ± 28 (340 ± 28)	328 ± 28 (622 ± 84)	3.62 ± 0.31	5.99 ± 0.16	40.4 ± 5.6	210
7c	134 ± 33 (405 ± 98)	276 ± 12 (909 ± 209)				
7d	6.8 ± 1.4 (42 ± 5)	11.5 ± 2 (80 ± 22)	0.21 ± 0.04	0.36 ± 0.01	10.4 ± 0.9	1500
7e	9.1 ± 0.2 (9.2 ± 0.5)	14 ± 1 (14 ± 1)			11.6 ± 1.5	1300
8	17 ± 1 (18 ± 1)	26 ± 3 (24 ± 1)			23.7 ± 0.4	1400
9a	300 ± 25 (266 ± 19)	635 ± 14 (495 ± 28)				
9b	158 ± 34 (162 ± 15)	300 ± 34 (327 ± 9)				
9c	125 ± 30 (134 ± 13)	270 ± 41 (259 ± 25)				
9d	29 ± 3 (25 ± 2)	39 ± 1 (35 ± 1)			93.8 ± 18.8	3200
10a	1870 ± 80 (1150 ± 130)	2530 ± 290 (1710 ± 40)				
10b	285 ± 9 (311 ± 7)	673 ± 56 (717 ± 113)				

[a] Concentrations required to inhibit growth of *T. brucei* and *T. cruzi* by 50% and 90%, respectively. IC_{50} and IC_{90} data are the mean of triplicate experiments ± SEM. [b] IC_{50} and IC_{90} data for the respective hydrochloride are shown in parentheses. [c] Cytotoxicity was determined by establishing the concentration required to inhibit growth of cultured L6 cells by 50% (IC_{50}) (Supporting Information). Data are the mean of triplicate experiments ± SEM. [d] Selectivity indices were calculated as the ratio of the IC_{50} for L6 cells to IC_{50} for *T. brucei*.

the presence of 1,1′-carbonyldiimidazole (CDI) in THF led to the corresponding *O*-benzyl hydroxamates **32**−**36**, **42**, **60**−**63**, **72**, and **73** in yields 63−95%. Accordingly, the *O*-methyl hydroxamate analogue **45** was obtained by coupling the carboxylic acid **27** with *O*-methylhydroxylamine. The acetohydroxamic acid analogues **7a**−**e**, **8**, **9a**−**d**, **10a**, and **10b** were acquired in high yields (80−95%) upon hydrogenolysis of the respective *O*-benzyl hydroxamate derivatives. In a similar manner, **27** was reacted with benzyl hydrazinecarboxylate to afford, after removal of the protecting group by hydrogenolysis, the acetohydrazide analogue **44**.

The synthesis of the carboxylic acids **27**, **28**, and **56**, and 1-unsubstituted 2,6-DKPs **6a** and **64** (Scheme 1) has been described in our previously published protocol.[9] By employment of the same methodology, their respective structural analogues **29**−**31**, **57**−**59**, **37**−**39**, and **65** were further synthesized as part of this study.

For the synthesis of the N-methylated carboxylic acids **41**, **70**, and **71** (Scheme 1), the 2,6-DKPs **6a**, **64**, and **65** were subjected to reductive methylation with $CH_2O/NaCNBH_3$ to give in 80−92% yields the methyl analogues **6b**, **66**, and **67**, respectively. The latter compounds, upon reaction with benzyl bromoacetate in NaH/DMF, are converted to the corresponding N-methylated 2,6-DKP-1-acetic acid benzyl esters (**40**, **68**, and **69**) in 83−95% yields. The carboxylic acids **41**, **70**, and **71** were afforded in almost quantitative yield by catalytic hydrogenolysis of their respective benzyl esters.

The 1-functionalized acetamide analogue **43** (Scheme 1) was prepared from **17** by the sequence of cyclization and functionalization reactions described for the preparation of the benzyl esters **22**−**26** except that bromoacetamide was used instead of benzyl bromoacetate.

RESULTS AND DISCUSSION

We introduced an acetohydroxamic acid group ($CH_2CONHOH$) at the imidic nitrogen of the 2,6-DKPs **6a** and **6b**, with the aim of achieving trypanocidal activity, potentially through inhibition of an essential metalloenzyme. This modification resulted in **7a** and **7b** (Figure 1), which were synthesized and tested against bloodstream-form *T. brucei* in vitro. They exhibited trypanocidal activity in the nanomolar range [IC_{50}(**7a**) = 90 nM; IC_{50}(**7b**) = 193 nM (Table 1)], identifying these acetohydroxamic acid derivatives as promising lead compounds. We next generated derivatives in which the basic spiro carbocyclic 2,6-DKP-1-acetohydroxamic structure was retained. First, we modified the **7a** and **7b** structures by replacement of the spiro adamantane portion with less bulky and lipophilic spiro cyclooctanes or cycloheptanes, resulting in the cycloalkane congeners **9a**, **9b**, **10a**, and **10b**. A further modification involved incorporation of a methyl or benzyl substituent at the position between the basic nitrogen and carbonyl group in the spiro heterocyclic skeleton of the parent compounds **7a** and **9a**, leading to the alkyl substituted hydroxamate analogues **7c**−**e**, **8**, **9c**, and **9d**. These analogues were tested against bloodstream-form *T. brucei*. **7a**, **7b**, and **7d** were also tested against *T. cruzi* epimastigotes. The resulting IC_{50} and IC_{90} are shown in Table 1.

The newly synthesized hydroxamic acid derivatives were potently active against *T. brucei* in free base and hydrochloride forms, with IC_{50} ranging from 6.8 to 1870 nM and from 9.2 to 1150 nM, respectively. Compounds **7d**, **7e**, **8**, and **9d** were the most potent against African trypanosomes, with activity in the low nanomolar range (IC_{50s} = 6.8−29 nM, Table 1), while hydroxamates **7a**, **7b**, and **7d** were also significantly active against *T. cruzi* epimastigotes. To assess the role of the hydroxamic acid moiety in the activity of **7a**−**e**, **8**, **9a**−**d**, **10a**, and **10b**, we replaced the acetohydroxamate pharmacophore of **7a** with related functional groups such as acetamide (CH_2CONH_2), acetohydrazide ($CH_2CONHNH_2$), and *O*-methyl acetohydroxamate ($CH_2CONH\text{-}OCH_3$). These modifications resulted in **43**, **44**, and **45** (Scheme 1). We also selectively assessed some of their corresponding carboxylic acid precursors [**27**−**31**, **41**, **56**, **59**,

and **71** (Scheme 1)] and some additional spiro carbocyclic 2,6-DKP scaffold molecules [**37**−**39** and **64**−**67** (Scheme 1)]. These modifications resulted in a substantial loss of activity against bloodstream-form *T. brucei* (Table 2, Supporting Information), suggesting that the hydroxamic acid unit is indispensable for trypanocidal activity in this class of compounds.

Changing the adamantane component of structure **7a** for a cyclooctane (**9a**) or cycloheptane (**10a**) progressively decreased activity against *T. brucei* (Table 1). Compared with **7a**, the IC_{50} of cyclooctane **9a** is 3.3-fold lower (IC_{50} = 300 nM), whereas the cycloheptane analogue **10a** is 21-fold less active (IC_{50} = 1870 nM). This marked loss of activity demonstrates the negative effect of reducing the bulkiness and lipophilicity of the carbocyclic ring and identifies the cycloheptane-based spiro 2,6-DKP core as a less effective scaffold for the acetohydroxamate pharmacophore.

Introduction of a methyl substituent on the basic nitrogen atom of the respective spiro carbocyclic 2,6-DKP residue of the parent compounds **7a**, **9a**, and **10a** (N-methylation) led to a 2.1-fold decrease in potency for the *N*-methyladamantane analogue **7b**, while enhanced activity was observed in the cases of the cyclooctane and cycloheptane *N*-methyl counterparts **9b** and **10b**. They were 1.9 and 6.6 times more potent than the corresponding NH-analogues **9a** and **10a** (Table 1). A similar trend was observed when the methyl substituent was incorporated into the methylene carbon adjacent to the basic nitrogen atom of the 2,6-DKP ring (C-methylation) in **7a** and **9a**, resulting in the respective *C*-methyl analogues **7c** and **9c** with *S*-configuration of the created chiral carbon. Thus, **7c** was 1.5 times less active than **7a**, whereas **9c** was 2.4-fold more effective than **9a** (Table 1). Therefore, *N*- or *C*-methyl substitution on 2,6-DKP ring seems to enhance trypanocidal activity only in the context of the cyclooctane- or cycloheptane-containing acetohydroxamic acid analogues (**9b**, **9c**, and **10b**).

The addition of the bulky hydrophobic benzyl substituent to the same carbon of the adamantane parent **7a** yielded analogues that were unexpectedly potent against *T. brucei*, as exemplified by **7d** (*S*-enantiomer), **7e** (*R*-enantiomer), and **8** (racemic mixture) (Table 1). Enantiomers **7d** and **7e** and their racemic mixture **8** retained high potency, although the *S*-enantiomer was slightly more active [**7d** (IC_{50} = 6.8 nM); **7e** (IC_{50} = 9.1 nM); **8** (IC_{50} = 17 nM)]. Their activities in the free base form were 5.3−13 times higher than the parent **7a** and 8−20 times higher than their *C*-methyl analogue **7c**. A similar effect was observed when an analogous benzyl substitution was made to the cyclooctane parent **9a**, leading to **9d** (*S*-enantiomer). This derivative had 10 times more trypanocidal activity than **9a** and 4.3 times more than its *C*-methyl counterpart **9c** (Table 1). This large increase in potency for **7d**, **7e**, **8**, and **9d** must reflect the strongly favorable stereoelectronic and lipophilic effects exerted by the benzyl substituent in the binding site. The most potent derivatives (**7d**, **7e**, **8**) were also tested against cultured procyclic (insect form) *T. brucei*. These were found to be 10−50 times more resistant to the trypanocidal effects [**7d** (IC_{50} = 332 ± 25 nM); **7e** (IC_{50} = 106 ± 6 nM); **8** (IC_{50} = 285 ± 20 nM)]. This implies that the major target of these compounds may be less important in procyclics.

Some differences in activity against bloodstream-form *T. brucei* were detected between the free base and hydrochloride forms of four of the target compounds: **7b**−**d** and **10a** (Table 1). For **7b**, **7c**, and **7d**, their hydrochlorides displayed 1.8-, 3-, and 6.2-fold lower potency, respectively. In contrast, **10a**·HCl was 1.6 times more potent than the corresponding free base. Interestingly, the order of activity obtained with **7d**, **7e**, and **8** was different when tested as hydrochloride salts. **7d** (*S*-enantiomer) was less potent than **7e** (*R*-enantiomer) and **8** (racemic mixture) by a factor of 4.6 and 2.3, respectively [**7e**·HCl (IC_{50} = 9.2 nM); **8**·HCl (IC_{50} = 18 nM); **7d**·HCl (IC_{50} = 42 nM)]. The reason for this is unknown.

Adamantane-based **7a**, **7b**, and **7d** in free base form also proved to be significantly active against cultured *T. cruzi* epimastigotes, with an IC_{50} at low micromolar to submicromolar levels (0.21−5.51 μM) (Table 1). Interestingly, the pattern of activity of the *N*-methyl analogue **7b** was opposite that shown by *T. brucei*. It was 1.5-fold more potent against *T. cruzi* than the parent structure **7a**. As with *T. brucei*, *C*-benzyl substitution on **7a**, leading to **7d**, significantly improved activity against *T. cruzi*, providing a 26-fold increase relative to **7a**. The cytotoxicity of the most active compounds against mammalian cells was determined using the rat skeletal myoblast L6 cell line. These experiments showed that derivatives **7b**, **7d**, **7e**, **8**, and **9d** had IC_{50} in the 10−100 μM range and that mammalian cells were largely refractory to the effects of **7a** (Table 1). The resulting selectivity indices, which varied from 210 (**7b**) to >3600 (**7a**), were highly promising in terms of drug development.

The excellent trypanocidal activity obtained with the hydroxamate analogues **7a**−**e**, **8**, **9a**−**d**, **10a**, and **10b** demonstrates that lipophilic spiro carbocyclic 2,6-DKP scaffolds constitute valuable platforms for developing antitrypanosome agents, through an acetohydroxamate substitution on their imidic nitrogen. Coupling of these well-defined chemical entities results in strongly enhanced activity through synergism of their structural features. The corresponding scaffold molecules are substantially inactive [**6a**, **6b**, and **64**−**67**, Table 2 (Supporting Information)] or only slightly active (**37**−**39**, Table 2), and acetohydroxamic acid itself has little trypanocidal effect (IC_{50} = 680 μM, Table 2).

Replacement of the hydroxamic acid group greatly diminishes trypanocidal properties (Table 2), suggesting that this component is a requirement for activity. One possibility is that this class of compound acts by inhibiting a vital parasite metalloenzyme, through the metal ion binding action of this moiety. Within this mechanism, the structural features of the spiro heterocyclic scaffold would be required for high-affinity interactions, including hydrogen bonds and electrostatic and hydrophobic interactions. Additional studies are required to understand the exact mechanism of action of these acetohydroxamic acid-based trypanocidal agents and to identify their target within the parasite.

■ CONCLUSION

We have successfully transformed lipophilic spiro carbocyclic 2,6-DKP scaffolds into compounds that are active against *T. brucei* and *T. cruzi* by incorporating an acetohydroxamic acid moiety into their imidic nitrogen atom. This could act as a metal ion complexing functional group. Compounds **7d**, **7e**, and **8** show low nanomolar trypanocidal activity against bloodstream-form *T. brucei*, and **7a**, **7b**, and **7d** display significant activity against *T. cruzi*. Compound **7d**, based on scaffold molecule (*S*)-6-benzyl-3,5-dioxospiro[piperazine-2,2′-adamantane] (**37**), was the most active derivative against *T. brucei* and *T. cruzi* with IC_{50} of 6.8 nM and 0.21 μM, respectively. Importantly, these compounds had very favorable selectivity indices when their activities against trypanosomes and mammalian cells were compared. Because of their potent antitrypanosome effect, the novel spiro carbocyclic 2,6-DKP-1-acetohydroxamic acids represent lead structures for the development of new treatments against African and American trypanosomiasis.

dx.doi.org/10.1021/jm200217m |*J. Med. Chem.* 2011, 54, 5250–5254

EXPERIMENTAL SECTION: CHEMISTRY

General. The purities of the tested compounds were determined by elemental analysis. The results obtained correspond to >95% purity (Supporting Information, Table 3).

General Procedure for the Preparation of the Hydroxamic Acids 7a−e, 8, 9a−d, 10a, and 10b. A solution of the appropriate *O*-benzyl hydroxamate (1 mmol) in absolute EtOH (40 mL) was hydrogenated (Pd−C 10%, 45 mg) for 3 h at room temperature and 50 psi. The catalyst was filtered off, washed with EtOH (3 × 10 mL), and the combined filtrates were evaporated in vacuo. Purification of the residue by column chromatography on silica gel using AcOEt−MeOH 5:1 (**7a**, **7b**, **9a**) or AcOEt (**7c−e**, **8**, **9b−d**, **10a**, **10b**) provided the pure hydroxamic acid as a white crystalline or foamy solid (Supporting Information).

ASSOCIATED CONTENT

Supporting Information. Synthesis details of **7a−e**, **8**, **9a−d**, **10a**, **10b**, **43−45**, **14**, **19**, **24**, **29**, **32**, **37**, **6b**, **40**, **41**, **66**, **68**, and **70**; chemical and physical data; antitrypanosome action data of **43−45**, **27−31**, **41**, **56**, **59**, **71**, **6a**, **6b**, **37−39**, and **64−67**; biological assays; elemental analysis data of the tested compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

This work was partially supported by a research grant from the University of Athens, Greece (ELKE Account KA 70/4/7841). J.M.K. acknowledges the support of the Wellcome Trust (Grant No. 084175).

ABBREVIATIONS USED

2,6-DKP, 2,6-diketopiperazine; MMP, matrix metalloproteinase; HDAC, histone deacetylase; 5-LO, 5-lipoxygenase; *Tb*PGDH, *T. brucei* 6-phosphoglyconate dehydrogenase; 6-PGDH, 6-phosphoglyconate dehydrogenase; CDI, 1,1′-carbonyldiimidazole; SI, selectivity index

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