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Synthesis of bicyclic 1,4-thiazepines as novel anti-*Trypanosoma brucei brucei* agents†

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1,4-Thiazepines derivatives are pharmacologically important heterocycles with different applications in medicinal chemistry. In the present work, we describe the preparation of new bicyclic thiazolidinyl-1,4-thiazepines **3** by reaction between azadithiane compounds and Michael acceptors. The reaction scope was explored and the yields were optimized. The activity of the new compounds was evaluated against *Nippostrongylus brasiliensis* and *Caenorhabditis elegans* as anthelmintic models and *Trypanosoma brucei brucei*. The most active compound was **3l**, showing an EC₅₀ = 2.8 ± 0.7 μM against *T. b. brucei* and a selectivity index >71.

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Introduction

Parasitic diseases affect hundreds of millions of people worldwide and result in significant mortality and devastating social and economic consequences.¹ However, most of the drugs available are decades old and have several limitations, such as poor efficacy, toxicity and the emergence and spread of drug resistance. The scientific community is concerned about this problem and fortunately has showed an increasing interest in this field, including efforts to identify new targets leading to the development of potential drug candidates.² In this context, our recent research is focused on the preparation of discrete libraries designed against specific key targets of parasites and bacteria. These include the essential redox enzymes thioredoxin glutathione reductase (TGR) of platyhelminths,³ the cysteine protease expressed by *Trypanosoma cruzi* cruzipain,⁴ and the metallo-β-lactamase enzymes of bacteria.⁵

Over the past decade, the design and preparation of new libraries of compounds has been directed to increasing molecular diversity,⁶ representing a challenge for organic chemists.⁷ In this context, our group has previously prepared small libraries containing N, O- and S-fused heterocycles.^{3,8} In an earlier approach, we synthesized a novel bicyclic scaffold: thiazolidinyl-2,3,4,5-tetrahydro-1,4-thiazepine **3a**. The compound was prepared by condensation of azadithiane **1a** and dimethylacetylene-dicarboxylate **2a** through a domino process (see Scheme 1).^{9,10}

Thiazepinone and thiazepine derivatives are pharmacologically important compounds with potential applications in the treatment of cancer and inflammatory diseases.^{11,12} Benzothiazepines (A) are privileged scaffolds that exhibit interesting biological activities,¹³ thiazolothiazepines (B) and 1,3-thiazepine derivatives (C) have shown antiviral activity,¹⁴ see Fig. 1.

Thus, the thiazolidinyl-2,3,4,5-tetrahydro-1,4-thiazepines **3** are new and therefore unexplored bicycles that represent a promising scaffold for medicinal chemistry. Hence we designed and synthesized a library of bicyclic thiazolidinyl-1,4-thiazepines, introducing different functional groups at the N-moiety and/or at the ring substituents. A primary screening of compounds as potential antiparasitic agents against helminths and protozoa was undertaken.

Scheme 1 Previously prepared thiazolidinyl-thiazepine **3**, **3a**: R¹ = *n*-Bu.

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Fig. 1 Representative structures of 1,4- and 1,3-thiazepines with biological interest.

Results and discussion

In order to determine the best conditions for the preparation of thiazolidinyl-1,4-thiazepines **3** (Scheme 1), we prepared five azadithianes **1** to be used as starting materials. We selected primary amines bearing benzyl groups with EWG or EDG and aliphatic amines. The condensation of 1,4-dithiane-2,5-diol with primary amines in *p*-TsOH/EtOH at reflux gave the corresponding azadithianes **1** as a single product. Compounds **1b–f** were obtained in high to very high yields (64 to 93%), see Table 1.

Azadithianes **1b–f** were used as nucleophiles with different Michael acceptors in order to prepare thiazepines **3**.

Optimization of thiazepine **3** formation

The optimization was performed studying different reaction conditions. Variables included the catalyst, the solvent, the heating source and the temperature. To determine the optimal reaction conditions, benzyl-azadithiane **1b** and the commercially available diethylacetylene-dicarboxylate **2b** were used as starting materials, see Table 2.

The reaction was firstly performed in CH₂Cl₂ at room temperature and at reflux under conventional thermal heating (Table 2, entries 1 and 2). We then explored the use of microwave as a source of heating and MeCN as solvent, affording better yields (entry 3) compared to conventional heating. Finally a preliminary solvent screening was performed using microwave heating (Table 2, entry 4 to 6).

Solvent optimization included the use of halogenated solvents (ClCH₂CH₂Cl and CH₂Cl₂), polar protic solvents (CF₃CH₂OH, BuOH) and a polar aprotic solvent (MeCN). The best results were obtained using MeCN, a solvent with high dielectric constant and dipolar moment, affording **3b** in 47% yield.

Table 1 Synthesis of 2,5-dithio-7-azabicyclo[2.2.1]heptane **1**

Entry	R	Product	Yield%
1	Bn	1b	76
2	<i>p</i> -OMeBn	1c	64
3	<i>p</i> -ClBn	1d	85
4	<i>p</i> -FBn	1e	93
5	CH ₂ CH ₂ OH	1f	86
6	CH ₂ CH ₂ CH ₂ COOH	1g	13

Table 2 Solvent and temperature optimization for **3b** preparation

Entry	Solvent	Conditions	3b yield (%) ^a
1	CH ₂ Cl ₂	Overnight, rt	35
2	CH ₂ Cl ₂	4 h, reflux	40
3	MeCN	30', 78 °C, MW	47
4	ClCH ₂ CH ₂ Cl	30', 78 °C, MW	27
5	CF ₃ CH ₂ OH	30', 68 °C, MW	5
6	BuOH	30', 110 °C, MW	29

^a Isolated yield.

Once we selected the best solvent, we explored the influence of the catalyst in the reaction; results are shown in Table 3. Based on previous reports, we used a Lewis acid (CF₃SO₃Ag), different bases (DABCO and DMAP), PPh₃ and NH₄OAc as possible catalysts for the thia-Michael addition.¹⁵

We first assayed the reaction with no catalyst, obtaining **3b** in 36% yield (entry 1). While the use of CF₃SO₃Ag did not improve the yield of the reaction, NH₄OAc slightly increased the yield to 47%, see entry 3. The reaction in presence of catalytic PPh₃ gave 42% yield. The best results were obtained when using bases like DMAP or DABCO (0.1 eq.), leading to thiazepine **3b** in 57 and 67% yields respectively; see entries 5 and 6.

Taking these results together, it seems that nucleophilic assistance, in particular by basic-like catalysts (*i.e.* DABCO or DMAP) improve the addition reaction (see entries 3–6).

The polar nature of the solvent suggests the formation of charged species during the course of the reaction. As depicted in Scheme 2, we propose a mechanism based on a thiolate-iminium **I** formation *via* azadithiane ring opening. Polar aprotic solvents and temperature could favour the thiolate **I** formation see Scheme 2(a). The base could participate reacting with Michael acceptor **2**, affording intermediate **II**, see Scheme 2(b).¹⁵ Thiolate **I** would attack intermediate **II** affording zwitterion **III**, which could then be trapped through a 7-*endo-trig* cyclization to afford the bicyclic product **3** after elimination of the base. This cyclization is favoured according to Baldwin's rules.¹⁶

Table 3 Catalyst optimization for **3b** preparation

Entry	Catalyst	3b yield ^a (%)
1	No catalyst	36
2	CF ₃ SO ₃ Ag (0.04 eq.)	29
3	NH ₄ OAc (0.1 eq.)	47
4	PPh ₃ (0.2 eq.)	42
5	DMAP (0.1 eq.)	56
6	DABCO (0.1 eq.)	67

^a Yields were determined after column purification.

Scheme 2 Proposed mechanism for the formation of thiazolidinylthiazepine 3, (a) thiolate I formation. (b) Intermediate II formation.

We had previously proposed the structure of thiazolidinylthiazepine 3 based on the long-range W coupling between Ha and Hb ($^4J = 0.8$ to 1.0 Hz). In this paper we report the confirmation of the molecular structure of 3d by single crystal X-ray diffraction (Fig. 2).

Single crystals of compound 3d were obtained from saturated CH_2Cl_2 solution. Compound 3d crystallized in the centrosymmetric monoclinic $P2_1/n$ space group with one molecule of 3d in the asymmetric unit. Table S1 in the ESI† contains selected bond distances and angles while Table S2† contains the data collection and refinement details. The molecular structure confirms the insertion of $\text{C}=\text{C}$ fragment into one of the two $\text{S}-\text{C}(\text{N})$ bonds and therefore the formation of the seven-membered 1,4-thiazepine ring. Furthermore, as can be expected from the proposed mechanism, both enantiomers of 3d are observed in the crystal.

Study of the reaction scope

To study the scope and versatility of the reaction, we used different Michael acceptors 2, prepared by addition of lithium acetylenes to different aldehydes, followed by MnO_2 alcohol oxidation, see Scheme 3.¹⁷

We therefore proceed to study the reaction scope between different primary amines 1 (described in Table 1) and the prepared alkynes 2 as Michael acceptors, see Table 4.

As we can observe in Table 4, the reaction is versatile and occurs in presence of different Michael acceptors 2. When we used the symmetric diethyl acetylenedicarboxylate 2b (entries 1 to 4), the reaction occurred as expected, affording the corresponding thiazolidinylthiazepines 3 in high to very high yields. When we set up the reaction with alkynyl ketone 2c

Scheme 3 Synthesis of Michael acceptors 2.

(see Scheme 3), containing an ester moiety and a ketone, we observed thiazepines 3g and 3i in better yields (entries 6 and 8). This result was expected because the ketone has a more electrophilic centre that favours product formation. The best yield is observed in entry 6, using Michael acceptor 2c. No reaction was observed with 2e, probably due to the absence of a di-carbonyl system (entry 9).

Hybrids design and synthesis

Once we prepared the library of thiazepines 3b–i, we designed and synthesized hybrid compounds, which combine the thiazepine scaffold with a furoxan ring (Fig. 3). We selected furoxans as they are extremely valuable frameworks with interestingly biological properties against trypanosomatids and helminths. Recently Salinas and co-workers have reported furoxan-containing compounds that inhibit TGRs from *Fasciola hepatica* and *Echinococcus granulosus*, both classes of parasitic flatworms: trematoda and cestoda respectively.¹⁸ With respect to trypanosomatids, the furoxan scaffold is also present in compounds with activity against *T. cruzi*¹⁹ and *T. b. brucei*.²⁰

Furoxan 4 was prepared according to the general procedure described by Maloney group.²¹ Hybrid compounds were prepared according to Scheme 4.

Anthelmintic activity

1. Thioredoxin glutathione reductase (TGR) inhibition.

The selenoenzyme TGR was selected as molecular target because it is ubiquitous and indispensable for flatworm parasites,²² and because the furoxan moiety of our hybrid compounds had previously shown activity as TGR inhibitor.¹⁸ Prepared compounds were screened as potential inhibitors of TGR using an *in vitro* spectrophotometric assay. Tested at $50 \mu\text{M}$, none of the thiazepines and furoxan-hybrids shows significant inhibitory activity of the enzyme (Table 5).

Complementary, we also screened the prepared compounds against the nematodes *Nippostrongylus brasiliensis* and *Caenorhabditis elegans* as models for anthelmintic discovery. Both species are close relatives to hookworms and to *H. contortus*, one of the most pathogenic nematodes of ruminants²³ since all of them belong to nematode clade V.

2. N. brasiliensis LA. We assayed the library of thiazepines at $20 \mu\text{M}$, results are shown in Table 5. Compounds display only modest activity, the best performance was observed for thiazepine 3e, bearing a *p*-F benzyl group in R^1 (*N. brasiliensis* death of 47%).

3. C. elegans as a model for anthelmintic screening. Traditional screens that rely on parasitic worms are costly and

Fig. 2 ORTEP diagram of compound 3d.

Table 4 Study of the reaction scope using different Michael acceptors

Entry	R ¹	R ²	R ³	Prod	Yield ^a (%)
1	1b (R ¹ = Bn)	–OEt	–CO ₂ Et	3b	67
2	1c (R ¹ = <i>p</i> -OMeBn)	–OEt	–CO ₂ Et	3c	72
3	1d (R ¹ = <i>p</i> -ClBn)	–OEt	–CO ₂ Et	3d	75
4	1e (R ¹ = <i>p</i> -FBn)	–OEt	–CO ₂ Et	3e	61
5	1f (R ¹ = (CH ₂) ₂ OH)	–PhpCl	–CO ₂ Me	3f	41
6	1c (R ¹ = <i>p</i> -OMeBn)	–PhpCl	–CO ₂ Me	3g	83
7	1b (R ¹ = Bn)	–PhpCl	–CO ₂ Me	3h	34 ^b
8	1b (R ¹ = Bn)	(CH ₂) ₂ Ph	–CO ₂ Me	3i	65 ^b
9	1b (R ¹ = Bn)	–PhpCl	–2-Py	3j	NR ^c

^a Yields were calculated after purification. ^b Reaction conditions were CH₂Cl₂/*p*-TsOH, reflux. ^c NR = no reaction was observed.

Fig. 3 Designed furoxan-thiazepine hybrids 3l, 3m and 3o.

labor intensive. Recently, P. Roy and co-workers established *C. elegans*, a free-living nematode, as an effective and cost-efficient model system for anthelmintic discovery.²⁴ Compounds were screened at 100 μM, using a sensitive motility assay. The results are shown in Table 5. The compounds library did not show remarkable activity on this model.

In summary, we explored the anthelmintic activity of the library through three different model assays, but neither the thiazepine nor the hybrids were active.

Scheme 4 Preparation of hybrids 3l, 3m and 3o.

Anti-trypansomoma activity

The anti-trypansomoma activity of the thiazepines library was evaluated against the bloodstream form of *T. brucei brucei*, causative agent of Nagana disease of cattle and suitable model of *T. b. rhodesiense*, which causes acute human African trypanosomiasis. The compounds were screened at 30 μM and 5 μM and the % of parasite death determined by flow cytometry (Table 6). Compounds showing > 90% *T. brucei* death at 30 μM were selected for EC₅₀ determination against parasites and murine macrophages. The selectivity index was calculated as EC₅₀ macrophage/EC₅₀ *T. b. brucei*. *Trypanosoma brucei brucei* strain 427, cell line 449 (a kind gift of Dr. R. Luise Krauth-Siegel, Heidelberg University, Germany) and mouse macrophages from the cell line J774 (purchased from the American Type Culture Collection, ATCC® code TIB-67™) were used in the experiments.

Thiazepine scaffolds 3b–h evaluation. With the exception of 3f, all thiazepines exerted more than 50% parasite death when tested at 30 μM. Thiazepine 3f was the less active compound; the structural feature is the presence of a hydroxyethyl group instead of the benzyl group in the N bridge. This points out the importance of R¹ substituent for the activity, feature that could guide further exploration at this level. EC₅₀ of thiazepines 3b–e and 3g were determined, data shown in Table 6. The anti-trypansomoma activity of all the selected compounds is of the same order than that of the reference drug Nfx. Thiazepine 3d (R¹ = *p*-ClBn) was the best compound displaying an EC₅₀ = 8 μM. Thiazepines 3e and 3g were toxic for macrophages with selectivity index (SI) = 3.6 and 0.6 respectively. Interestingly, at 200 μM our best compound 3d lacked toxicity against macrophages (SI > 25).

Furoxan-hybrids 3l–o evaluation. Hybrids containing one furoxan ring 3l and 3m are both more active than Nfx and also more active than thiazepine 3d. If we compare hybrid 3m with its precursor thiazepine 3h, the first is 9-fold more active than the second when assayed at 5 μM. The introduction of furoxan rings in R¹ or R² is beneficial for the anti-trypansomoma activity. In contrast, compound 3o bearing two

Table 5 Anthelmintic evaluation of thiazepines **3b–h** and hybrids **3l**, **3m** and **3o**

Entry	Cmp	<i>N. brasiliensis</i> death % ^a [20 µM]	% TGR inhibition ^b [50 µM]	% <i>C. elegans</i> motility inhibition ^c [100 µM]
1	3b	5.9	0	20
2	3c	13.8	36	50
3	3d	17.1	0	37
4	3e	47.6	41	26
5	3f	20.6	0	18
6	3g	27.6	29	3
7	3h	20.5	0	51
8	3l	—	0	22
9	3m	—	0	—
10	3o	—	—	—
11	Abz	100	N/A	N/A
12	Iver	N/A	N/A	100
13	Aur	N/A	100	N/A

^a Death percentage of *Nippostrongylus brasiliensis* [L4] at [inh] = 20 µM. Albendazole EC₅₀ = 0.34 µM. ^b Percentage of thioredoxin glutathione reductase (TGR) inhibition (%) was measured at [inh] = 50 µM. Auranofin was used as reference, showing 85% inhibition at 30 nM. ^c *C. elegans* motility inhibition assay was performed at [inh] = 100 µM. Reference was performed with 2% DMSO, corresponding to 0% motility inhibition. N/A not assayed.

Table 6 Anti-*T. b. brucei* activity and selectivity of thiazolidinyl-thiazepines **3b–h** and furoxan-thiazepine hybrids **3l**, **3m** and **3o**. Values represent the mean ± SD (n = 3)

Comp	<i>T. brucei</i>			Macrophage	
	% death at 30 µM	% death at 5 µM	EC ₅₀ (µM)	EC ₅₀ (µM)	SI ^a
3b	98.8 ± 0.3	3.5 ± 3.7	18.9 ± 2.6	200 ± 11	10
3c	97.7 ± 0.3	3.0 ± 0.5	18.0 ± 2.0	>200	> 11
3d	97.3 ± 0.4	2.4 ± 1.2	8.0 ± 0.4	> 200	> 25
3e	99.4 ± 0.1	12.7 ± 1.7	17.8 ± 3.7	64.4 ± 3.5	3.6
3f	3.6 ± 1.2	1.8 ± 5.7	—	—	—
3g	95.9 ± 0.6	0 ± 5.0	16.4 ± 1.5	9.7 ± 0.6	0.6
3h	57.5 ± 2.2	3.4 ± 13.4	—	—	—
3l	97.8 ± 0.5	60.4 ± 1.2	2.8 ± 0.7	> 200	> 71
3m	97.7 ± 0.1	89.4 ± 2.1	2.5 ± 0.2	3.1 ± 0.5	1.2
3o	23.3 ± 1.1	12.2 ± 2.2	—	—	—
Nfx	—	—	15 ± 3	150 ± 5	10

^a Selectivity index = EC₅₀ macrophage/EC₅₀ *T. b. brucei*.

Table 7 Lipinski's parameters^a for thiazepines **3** and % *T. b. brucei* death at 30 µM

Entry	Comp	log <i>P</i>	MW	HBD	HBA	% death [30 µM]
1	3b	2.8	393	0	5	98.8 ± 0.3
2	3c	2.68	423	0	6	97.7 ± 0.3
3	3d	3.36	427	0	5	97.3 ± 0.4
4	3e	2.96	411	0	5	99.4 ± 0.1
5	3f	1.82	399	1	6	3.6 ± 1.2
6	3g	3.95	475	0	6	95.9 ± 0.6
7	3h	4.07	445	0	5	57.5 ± 2.2
8	3l	3.57	563	0	10	97.8 ± 0.5
9	3m	5.48	605	0	7	97.7 ± 0.1
10	3o	4.93	685	0	11	76.7 ± 1.1

^a Calculated according to the method of Ghose, Pritchett and Crippen in Spartan 10.

furoxan rings at R² and R³ is inactive, which suggests that introducing a furoxan at position R³ is detrimental for activity.

The hybrids **3l** and **3m** were selected to determine EC₅₀ in *T. b. brucei* (EC₅₀ = 2.8 ± 0.7 µM and EC₅₀ = 2.5 ± 0.2 µM respectively), see Table 6.

Strikingly, while **3l** lacked cytotoxicity at 200 µM, **3m** resulted highly toxic to macrophages (EC₅₀ = 3.1 µM). Compound **3l** displayed the highest selectivity against *T. brucei* (SI > 71).

Drug-like properties

Finally, we calculated Lipinski parameters²⁵ to analyse the chemical and physical properties of the thiazepine library and evaluate its druglikeness (Table 7).

Thiazepines **3b–h** follow the rule of 5: log *P* under 5, MW under 500 Dalton, HBA < 10 and HBD < 5. This suggests that bicyclic scaffolds would have good bioavailability when administered orally, which could encourage the exploration of other relevant biological activities for these compounds.

The compound with the best inhibition profile **3l** breaks one of the rules (MW). Nonetheless, there is a significant number of drugs in the 500 < MW < 600 range; molecules are still considered drug-like despite breaking one of the rules. According to Roughley's analyses, 36% of drugs break at least one rule.²⁶

Conclusions

In conclusion, we optimized the synthesis of thiazepines **3**, using DABCO as catalyst and microwave heating. X-Ray single-crystal diffraction confirmed the bicyclic structure of compound **3b** and a mechanism for the base catalysis was proposed.

We were able to prepare a small library of thiazolidinyl-thiazepines **3b–h** and furoxan-hybrids **3l**, **3m** and **3o**, whose antiparasitic activity was evaluated against four different targets. Thiazepine scaffolds **3b–d** show good activity against

the infective form of *T. b. brucei* and low cytotoxicity against murine macrophages, the best compound was **3d** ($EC_{50} = 8.0 \pm 0.4$ and $SI > 25$). Hybrids **3l** and **3m** bearing one furoxan ring in different positions, present the highest potency ($EC_{50} = 2.8 \pm 0.7$ and $2.5 \pm 0.2 \mu M$ respectively). Taking into account the cytotoxicity against a mammalian cell model, the most selective compound is **3l** with an excellent $SI (>71)$.

These results are encouraging due to the good anti-*T. b. brucei* activity and the novelty of the thiazepine scaffold. Compound **3d** and derivatives could be used as leaders for further studies against trypanosomatids.

Conflicts of interest

There are no conflicts to declare.

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