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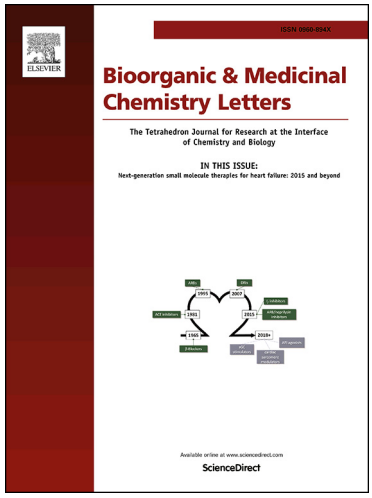
Published in:
Bioorganic & Medicinal Chemistry Letters

DOI:
10.1016/j.bmcl.2018.08.005

Publication date:
2018

Document Version
Peer reviewed version



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PII: S0960-894X(18)30668-1
DOI: https://doi.org/10.1016/j.bmcl.2018.08.005
Reference: BMCL 25985

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 5 June 2018
Revised Date: 25 July 2018
Accepted Date: 3 August 2018

Please cite this article as: Thomas, M.G., De Rycker, M., Cotillo Torrejon, I., Thomas, J., Riley, J., Spinks, D., Read, K.D., Miles, T.J., Gilbert, I.H., Wyatt, P.G., 2,4-Diamino-6-methylpyrimidines for the potential treatment of Chagas' Disease, *Bioorganic & Medicinal Chemistry Letters* (2018), doi: https://doi.org/10.1016/j.bmcl.2018.08.005

2,4-Diamino-6-methylpyrimidines for the potential treatment of Chagas' Disease

Michael G Thomas,[a] Manu De Rycker,[a] Ignacio Cotillo Torrejon,[b] John Thomas,[a] Jennifer Riley,[a] Daniel Spinks,[a] Kevin D Read,[a] Tim J Miles,[b] Ian H Gilbert[a] and Paul G Wyatt [a]

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Abstract: Chagas' disease, caused by the protozoan parasite *Trypanosoma cruzi,* affects 8-10 million people across the Latin American population and is responsible for around 12,500 deaths per annum. The current frontline treatments, benznidazole and nifurtimox, are associated with side effects and lack efficacy in the chronic stage of the disease, leading to an urgent need for new treatments. A high throughput screening campaign against the physiologically relevant intracellular form of the parasite identified a series of 2,4-diamino-6-methylpyrimidines. Demonstrating the series did not work through the anti-target *Tc*CYP51, and was generally cytocidal, confirmed its suitability for further development. This study reports the optimisation of selectivity and metabolic stability of the series and identification a suitable lead for further optimisation.

Chagas' Disease[1], an infection caused by the parasite *Trypanosoma cruzi*, is endemic in 21 countries across Latin America and is estimated to be responsible for around 12,500 deaths per Annum[2]. The disease is also found in many other parts of the world, mainly due to migration. Chagas' disease is characterized by an initial acute phase, which is fatal for around 5% of children. This is followed by a long-term chronic phase, which can eventually be fatal due to associated cardiac problems[3,4]. The standard treatment is based on benznidazole and nifurtimox, nitro-aromatic drugs that effectively clear parasites in the acute phase, but are less effective in the chronic phase[5]. There are no current alternatives to benznidazole or nifurtimox and recent clinical trials of posaconazole, an inhibitor of the enzyme *T. cruzi* C14 α-demethylase (commonly known as *Tc*CYP51) did not give promising results[6]. Thus, there is an urgent need for novel chemical classes that target *T. cruzi* through alternative mechanisms to *Tc*CYP51.

To this end, we have developed a screening cascade to identify chemical series with the potential to treat Chagas' disease (see fig. 1)[7]. An initial high throughput phenotypic screen against the intracellular amastigote form of *T. cruzi* identified compounds that inhibit parasite growth with selectivity over host Vero cells[7]. These compounds were then counter-screened against *Tc*CYP51 to identify those acting *via* alternative, non-*Tc*CYP51 mechanisms[8]. Alongside this, a second *T. cruzi* assay identified compounds acting through a cytocidal, rather than cytostatic mode of action[7]. Series thus identified could be further optimized to give compounds suitable for progression into an *in vivo* efficacy model of Chagas' disease.

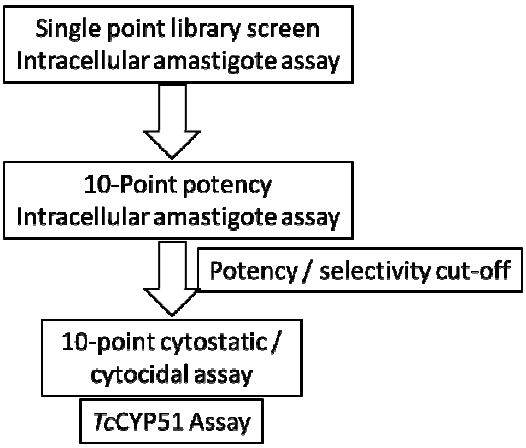
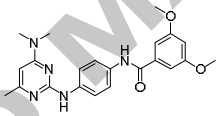


Figure 1: Screening cascade to identify chemical series for development against *T. cruzi*

A set of >13,000 compounds with antimalarial activity was released by GSK (referred to as TCAMS)[9], and this set was screened through the cascade described. One of the series identified from this screen was exemplified by compound **1** (Table 1), which demonstrated a pEC_{50} against *T. cruzi* parasites of 6.9 and a 40-fold selectivity window *versus* host Vero cells. Compound **1** was further profiled through the highlighted cascade, showing cytocidal behavior and no *Tc*CYP51 activity (*i.e.* pEC_{50} <5). In terms of *in vitro* DMPK properties, the compound had low kinetic solubility but was stable in mouse liver microsomes (MLM). Further examination of the hit set identified a number of close analogues that all contained the 1,4-dianilino moiety, with either amide or sulfonamide linkers, which further validated this series. These analogues all had a relatively similar selectivity window *versus* the host cells (40-60 fold) and poor solubility (data not shown). This programme therefore focused on optimizing potency, selectivity and solubility to identify compounds suitable for progression into an *in vivo* model of Chagas' disease.

Table 1. **Hit Compound** 1**.**

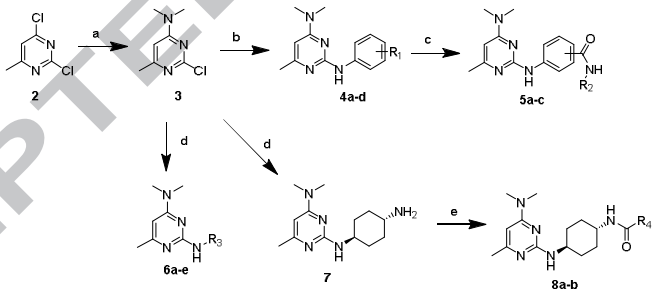


No.	*Tc* pEC_{50} [a]	Vero pEC_{50} [a]	Selectivity [b]	Solubility µM [c]	Cl_{int} (MLM) ml/min/g [d]	*Tc*CYP51 pIC_{50}	Cytocidal
1	6.8±0.2	5.2±0.3	40	20	0.7	<5	Yes

[a] *Tc* refers to activity in *T. cruzi* amastigote cultures in Vero cells. pEC_{50} value shown as mean values from three EC_{50} determinations ± standard deviation. [b] Selectivity refers to Vero pEC_{50}/Tc pEC_{50}. [c] Kinetic solubility measured in water from a DMSO solution of compound. [d] Cl_{int} (MLM) refers to intrinsic clearance measured in mouse liver microsomes

This 2,4-diamino-6-methylpyrimidine motif has previously been reported to show antimalarial activity[10] and has more recently been identified in screens against the kinetoplastids[11]. As far as we are aware, this is the first report of developing this compound series for the treatment of Chagas' disease.

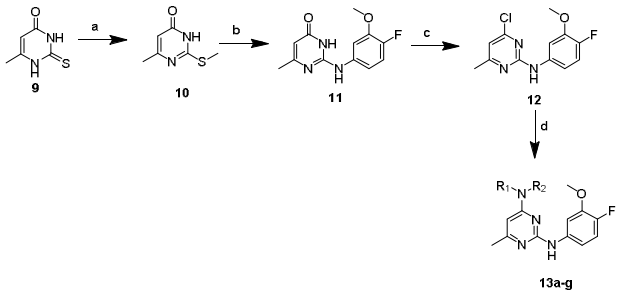
Chemistry to access the desired analogues is described in Schemes 1-3. Compounds with variations in the 2-pyrimidinyl position were synthesized according to Scheme 1[10]. Commercially available 2,4-dichloro-6-methylpyrimidine **2** was treated with dimethylamine, followed by a suitably substituted aniline to give compounds **4a-d**, whilst treatment with *m*- or *p*-aminobenzoate, followed by hydrolysis of the ester, gave acids that were treated with TBTU and a relevant amine to give amides **5a-c**. Compound **3** could also be reacted with alkyl amines under basic conditions to give compounds **6a-e**, whilst treatment with 1,4-*trans*-cyclohexanediamine and subsequent acylation gave **8a-b**. Compounds **18a-e** could be synthesized following an identical route, starting from suitably functionalized 2,4-dichloropyrimidines.



Scheme 1. Synthesis of **4a-d**, **5a-c, 6a-e** and **8a-b**. (a) Me_2NH, THF, 68%; (b) Aniline, $Pd(^tBu_3P)_2$, NaO^tBu, 1,4-dioxane, 120^oC, 21-68%; (c) 1M NaOH, THF then TBTU, DIPEA, DMF; (d) 1,4-dioxane, 160^oC; (e) R_4-COCl, DIPEA, DCM.

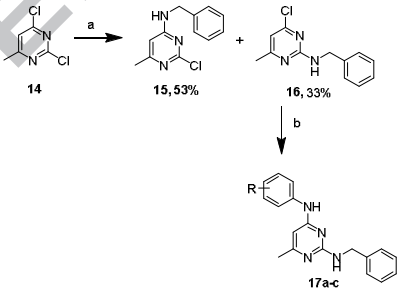
Analogues with variations to the pyrimidinyl 4-position were synthesised according to Scheme 2. The thiopyrimidine **9** was alkylated with iodomethane and the resulting thioether

displaced by 3-methoxy-4-fluoro aniline to give **11**. This was treated with $POCl_3$ and the resulting chloro-group displaced by relevant amines to give compounds **13a-g**.



Scheme 2. Synthesis of **13a-g.** (a) Iodomethane, potassium carbonate, DMSO, 48%; (b) Aniline, butan-1-ol, 110°C, 49%; (c) $POCl_3$, 120°C, 59%; (d) R_1R_2-NH_2, DIPEA, 1,4-dioxane, 110°C

In order to access 2-benzylamino-4-anilino compounds, 2,4-dichloro-6-methyl pyrimidine **14** was treated with benzylamine, giving a mixture of the 2- and 4- substituted intermediates (**15** and **16**), which were easily separated and identified by NMR (Scheme 3). Compound **16** was treated with 3-methoxy-4-fluoroaniline under acidic conditions to give **17a-c**.



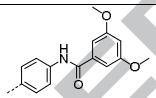
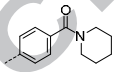
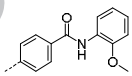
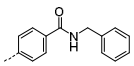
Scheme 3. Synthesis of **17a-c**. (a) Benzylamine, DIPEA, THF (b) relevant aniline, conc. HCl, EtOH, 50%.

The focus of the initial medicinal chemistry program was to improve solubility and selectivity, targeting a pEC_{50} > 7 and cellular selectivity of > 100-fold in the intracellular amastigote assay[7], solubility of > 250 µM and Cl_{int} < 5 ml/min/g. These parameters were based on previous experience of progressing compound series into *in vivo* models of Chagas' disease[12]. Since this series was identified through a phenotypic screen, the molecular target

was unknown; therefore we undertook a systematic exploration of the pyrimidine substituents to address the progression parameters.

An initial strategy was to remove / replace the 1,4-dianilino moiety, which we believed could be a key driver of the poor solubility of **1,** as well as presenting potential genotoxicity risks as the compound series progressed. Also, removal of the benzamide would reduce the number of aromatic rings, which could also help to improve solubility. The initial round of synthesis investigated whether either aminobenzamides or other substituted anilines would result in improved profiles (Table 2). The *para*-substituted piperidine amide **5a** showed no toxicity against the host cells at the top concentration tested (50 µM), but had reduced potency compared to compound **1**. Phenyl and benzyl amides, as exemplified by **5b** and **5c**, had a similar potency but reduced selectivity compared to **5a**. Further exploration of the benzamides, including meta-substituted benzamides, failed to improve potency.

Table 2: *In vitro* profile of analogues **5a-c**, **4a-d** and **6a-c**.

No.	R	Tc pEC_{50} [a]	Vero pEC_{50} [a]	Selectivity [b]	Solubility µM [c]	Cl_{int} (MLM) ml/min/g [d]
1		6.8±0.2	5.2±0.3	40	20	0.7
5a		5.7±0.3	<4.3	>25	N/A	N/A
5b		6.1±0.2	6.2±0.4	1.3	N/A	N/A
5c		5.9±0.4	5.3±0.3	4	N/A	N/A
4a		5.8±0.3	<4.3	>32	>250	10
4b		6.1±0	<4.3	>63	>250	15

4c		5.9±0.3	<4.3	>40	>250	14
4d		6.4±0.1	4.5±0.1	80	>250	17
6a		5.5±0.3	<4.3	>16	>250	28
6b		5.9±0.1	<4.3	>40	>250	11
6c		6.0±0.3	4.6±0.2	25	>250	12

[a] *Tc* refers to activity in *T. cruzi* amastigotes cultures in Vero cells. pEC_{50} values are shown as mean values from two EC_{50} determinations ± range (except **1, 4b** where value is ± standard deviation from >2 determinations). [b] Selectivity refers to Vero pEC_{50}/Tc pEC_{50}. [c] Kinetic solubility measured in water from a DMSO solution of compound. [d] Cl_{int} (MLM) refers to intrinsic clearance measured in mouse liver microsomes. N/A means value was not measured

Because the strategy of replacing the anilide with a benzamide had not led to improved compounds, we investigated a wider range of substituted anilines (exemplified by **4a-d** in Table 2). Pleasingly, both m- and p-methoxy analogues (**4a** and **4b**) showed similar potencies to compounds **5a-c** with an improved selectivity window and solubility compared to **1**. Alongside potency, microsomal clearance for **4a** and **4b** required further optimization; hence we synthesized further substituted anilines and benzylamines to address these issues. All attempts, as exemplified by **4c**, **4d**, and **6a-c** led to analogues with similar potency and clearance values.

As we had made a significant change to the original hit scaffold, we confirmed that compounds **4d** and **6a** did not inhibit *Tc*CYP51 and both were cytocidal. Alongside that, profiling of **4d** in a panel of potential off target receptors associated with *in vivo* toxicity, revealed that inhibition of hERG (pIC_{50} 5.3) was a potential issue, due to its association with potentially fatal arrhythmia. This data did not stop the progression of the series, but would need addressing if the compound series were ultimately to be developed.

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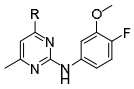
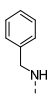
Encouraged by **4d** and **6a**, which were highly selective and soluble, further SAR was explored around these scaffolds to improve metabolic stability (See Tables 3 and 4) by removing the potential for *N*-demethylation of the 4-dimethylamino group. Analogues of **4d**, represented by **13a-g** (Table 3), where the dimethylamine was replaced with other alkyl amines, failed to significantly improve metabolic stability (where Cl_{int} <5ml/min/g was targeted). Additionally, none of the changes, which introduced both polar and non-polar groups, led to a significant improvement in potency.

Table 3: In vitro profile of analogues **13a-g.**

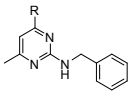


No.	R	Tc pEC_{50} [a]	Vero pEC_{50} [a]	Selectivity [b]	Solubility µM [c]	Cl_{int} (MLM) [d] ml/min/g
4d		6.4±0.3	4.5±0.1	80	>250	17
13a		6.0±0.4	4.8±0.2	16	160	17
13b		6.5±0.5	4.7±0.2	63	220	14
13c		5.1±0.4	<4.3	>6	>250	18
13d		5.8±0.3	4.6±0.2	16	>250	35
13e		5.1±0.2	4.4±0.1	5	219	N/A
13f		5.1±0.2	4.5±0.2	4	>250	35
13g		6.1±0.5	5.3±0.2	6.3	>250	8

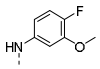
[a] *Tc* refers to activity in *T. cruzi* amastigote cultures in Vero cells. pEC_{50} value shown as mean values from three EC_{50} determinations ± standard deviation. [b] Selectivity refers to Vero pEC_{50}/Tc pEC_{50}. [c] Kinetic solubility measured in water from a DMSO solution of compound. [d] Cl_{int} (MLM) refers to intrinsic clearance measured in mouse liver microsomes

To further explore replacement of the 4-dimethylamino group, we focused on the introduction of substituted anilines. Due to concern that addition of a further aromatic ring could reduce solubility, these changes were introduced onto the benzyl substituted scaffold of **6a**, rather than the aniline **4d**, where the increased sp^3 character might alleviate this potential issue[13]. As shown in Table 4, these analogues (**17a-c**) demonstrated improved potency whilst maintaining selectivity and solubility compared to compound **6a**, although none of them improved the metabolic stability. **17c** did show a significant improvement in potency compared to **6a**, achieving our target of pEC_{50} > 7.0, and also contained significant structural changes. Because of this, **17c** was further profiled in our cytostatic / cytocidal assay where it demonstrated cytostatic behavior, suggestive of a change in the mode of action of this compound. This was undesirable, because our previous experience of a cytostatic compound was that it would not achieve cures in *in vivo* models[12]. As such, this sub-series was not progressed further.

Table 4: *In vitro* profile of analogues **17a-c.**



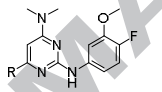
No.	R	Tc pEC_{50} [a]	Vero pEC_{50} [a]	Selectivity [b]	Solubility µM [c]	Cl_{int} (MLM) ml/min/g [d]
6a		5.5±0.3	<4.3	>16	>250	28
17a		6.4±0.4	5.1	20	>250	10
17b		6.7±0.1	5.1±0.1	40	>250	20

17c		7.1±0.4	5.3±0.1	63	180	10

[a] *Tc* refers to activity in *T. cruzi* amastigotes cultures in Vero cells. pEC_{50} values are shown as mean values from three or more EC_{50} determinations ± standard deviation. [b] Selectivity refers to Vero pEC_{50}/Tc pEC_{50}. [c] Kinetic solubility measured in water from a DMSO solution of compound. [d] Cl_{int} (MLM) refers to intrinsic clearance measured in mouse liver microsomes

Returning to the 2-(3-methoxy-4-fluoroanilino)-4-dimethylamino template of **4d,** which retained the same *in vitro* profile as compound **1**, we investigated variations to the 6-methyl group (Table 5), focusing on changes which could enhance metabolic stability. As can be seen from Table 5, all analogues investigated demonstrated a significant reduction in potency although **18e** was the first compound in the series to demonstrate progressable metabolic stability.

Table 5: In vitro profile of analogues **18a-e**.



No.	R	Tc pEC_{50} [a]	Vero pEC_{50} [a]	Selectivity [b]	Solubility µM [c]	Cl_{int} (MLM) ml/min/g [d]
4d		6.4±0.3	4.5±0.1	80	>250	17
18a		5.4±0.1	<4.3	>13	160	29
18b		5.1±0.1	<4.3	>6	>250	35
18c		5.7±0.3	<4.3	>25	170	50
18d		4.6±0.5	<4.3	>2	110	N/A
18e		4.5±0.2	<4.3	>1.6	>250	3.4

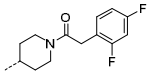
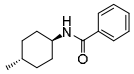
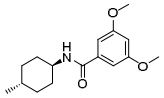
[a] *Tc* refers to activity in *T. cruzi* amastigotes cultures in Vero cells. pEC_{50} values are shown as mean values from three or more EC_{50} determinations ± standard deviation. [b] Selectivity refers to Vero pEC_{50}/Tc pEC_{50}. [c] Kinetic solubility measured in water from a DMSO solution of compound. [d] Cl_{int} (MLM) refers to intrinsic clearance measured in mouse liver microsomes. N/A means value was not measured

As variations to the 4- and 6-positions of the pyrimidine had failed to identify compounds with suitable profiles to progress to *in vivo* studies, our focus returned to the pyrimidinyl 2-position. From previous SAR (outlined within Table 1 and 2) it was known that variations in this position could be tolerated without loss of potency. Also, **18e** gave us optimism that analogues with improved metabolic stability could be identified within the series.

Table 6 shows a comparison of these analogues with **4d** and **6a**, where we were able to identify compounds with a similar level of potency, solubility and selectivity. Critically we observed a significant improvement in metabolic stability, most notably for compound **8b**. This compound had a pEC_{50} of 6.4 as well as very good selectivity (100-fold) and solubility, and no activity versus *Tc*CYP51. Compound **8b** was also cytocidal, albeit with a narrow selectivity window; this lower selectivity likely being due to the two assays being run in different cell lines. Finally **8b** was profiled against the same panel of off target receptors that was used for **4d**, unfortunately showing no improvement. In fact, further risks were identified; hERG (pIC_{50} 5.4), Aurora B (pIC_{50} 7.4, highlighting potential promiscuity issues with other kinases) and CB1 (pIC_{50} 7.2, concerns of psychotropic effects). These changes demonstrated that the cyclohexyldiamine linker gave a scaffold with the potential for further modifications to improve the profile against *T. cruzi*, but introduced potential toxicity risks which could hamper the development of this series.

Table 6*: In vitro* profile of analogues **4d**, **6a**, **6d-e** and **8a-b**.

No.	R	Tc pEC_{50} [a]	Vero pEC_{50} [a]	Selectivity [b]	Solubility µM [c]	Cl_{int} (MLM) ml/min/g [d]
4d		6.4±0.3	4.5±0.1	80	>250	17
6a		5.5± 0.3	<4.3	>16	>250	28
6d		4.8±0.1	<4.3	>3	>250	3.8

6e		5.5±0.1	<4.3	>16	N/A	N/A
8a		5.9±0.2	<4.3	>40	>250	N/A
8b		6.4±0.4	4.4±0.1	100	>250	4.2

[a] *Tc* refers to activity in *T. cruzi* amastigotes cultures in Vero cells. pEC_{50} values are shown as mean values from three or more EC_{50} determinations ± standard deviation. [b] Selectivity refers to Vero pEC_{50}/Tc pEC_{50}. [c] Kinetic solubility measured in water from a DMSO solution of compound. [d] Cl_{int} (MLM) refers to intrinsic clearance measured in mouse liver microsomes. N/A means value was not measured

In summary, a novel series of *T. cruzi* inhibitors was identified through high throughput screening against the intracellular parasite that were demonstrated to be cytocidal, and also to be working via a non-*Tc*CYP51 mechanism. These initial hits suffered from poor selectivity and low solubility and microsomal stability. A series of compounds was therefore synthesized to address these concerns. The initial rounds of optimisation produced compound **17c**, with acceptable potency and improved solubility and selectivity. However, **17c** was no longer cytocidal, suggesting that its mode of action had changed, and also highlighting the need to use *Tc*CYP51 and cytocidality assays when working on a series where the mode of action was unknown. A different approach of using non-aromatic linkers to mimic the dianilino moiety of the initial hits led to **8b**; this compound was moderately potent (pEC_{50} 6.4), highly selective over the host Vero cells and displayed improved microsomal stability, albeit with increased off-target risks leading to the potential for *in vivo* toxicity. As the series was progressed phenotypically, it could potentially show polypharmacology, with different molecules having varying inhibition profiles, making optimisation challenging. Although further exploration of the scaffold could give compounds with suitable profiles for progression to *in vivo* studies, knowledge of the molecular targets and binding mode(s) of the series would facilitate this optimisation against targets which are cytocidal, and also offer strategies to design out off-target effects.

Acknowledgements

We would like to acknowledge the Wellcome for funding (**092340** and **100476**). The authors thank Gina MacKay for performing HRMS analyses and for assistance with performing other NMR and MS analyses; Michelle Wantoch, David Standing, Nicole Chapman, Metul Patel, Katrina Soor, Lucy Otter and Laurie Gordon for profiling **4d** and **8b** against the panel of potential off target receptors; Alastair Pate and Francesco Gastaldello for data management.

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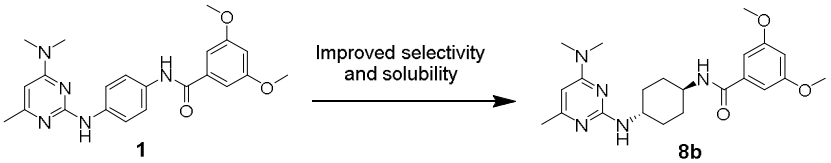
Optimising selectivity and metabolic stability of anti-Chagas disease pyrimidines

Structure activity relationships development to optimise developability properties

Development of compound not targeting *T. cruzi* C14 α-demethylase



1

pEC_{50} vs. *T cruzi* = 6.8
Selectivity *vs.* host cell = 40
Aqueous solubility = 20 μM

8b

pEC_{50} vs. *T cruzi* = 6.4
Selectivity *vs.* host cell = 100
Aqueous solubility > 250 μM