Lead Optimisation of Pan-Trypanosomatid Inhibitors Inspired by Nature

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Introduction

Neglected Tropical Diseases

The World Health Organization (WHO) classifies twenty diverse conditions, mainly found in tropical areas, as neglected tropical diseases (NTDs)[1]. These affect more than one billion people[1], mainly in impoverished communities in rural areas, partially because these lack adequate access to clean water, sanitation, and appropriate housing[2]. NTDs include Chagas disease, leishmaniases, schistosomiasis, dengue and chikungunya, and onchocerciasis[1]. The diseases have severe health, social, and economic consequences for those infected[1]. This research project focused on the drug development against human African trypanosomiasis (sleeping sickness).

Human African Trypanosomiasis

Trypanosomatida are a group of kinetoplastid protozoan parasites[3] causing African sleeping sickness, chagas disease, and leishmaniases[4]. Human African trypanosomiasis (HAT) is caused by two parasites: *T. brucei gambiense* and *T. brucei rhodesiense*[4]. Transmission occurs through infected tsetse flies (glossina), which previously acquired the parasites from infected humans or animals[5] (Figure 1[6]). The NTD is endemic in 36 countries of sub-Saharan Africa[2], with the *T. b. gambiense* form of the disease being responsible for 92% of reported cases (found in 24 countries) and the *T. b. rhodesiense* form being responsible for the remaining 8% of reported cases (found in 13 countries)[5]. The widely spread *T. b. gambiense* causes a chronic illness that progresses slowly, where people can be infected for years without showing major signs or symptoms[2,5]. However, when these do emerge, the disease is often already advanced, having crossed the blood-brain barrier and infected the central nervous system. This leads to obvious late-stage signs of HAT including behavioural changes, neurological decline, and daytime somnolence and nocturnal insomnia[2,5]. *T. b. rhodesiense* is an acute form of HAT, developing rapidly with early-stage symptoms including headaches, fever, and lymphadenopathy (enlarged posterior cervical lymph nodes) and then progressing to the late-stage severe symptoms like those of the chronic form. Both forms of HAT are fatal when left untreated[2,5].

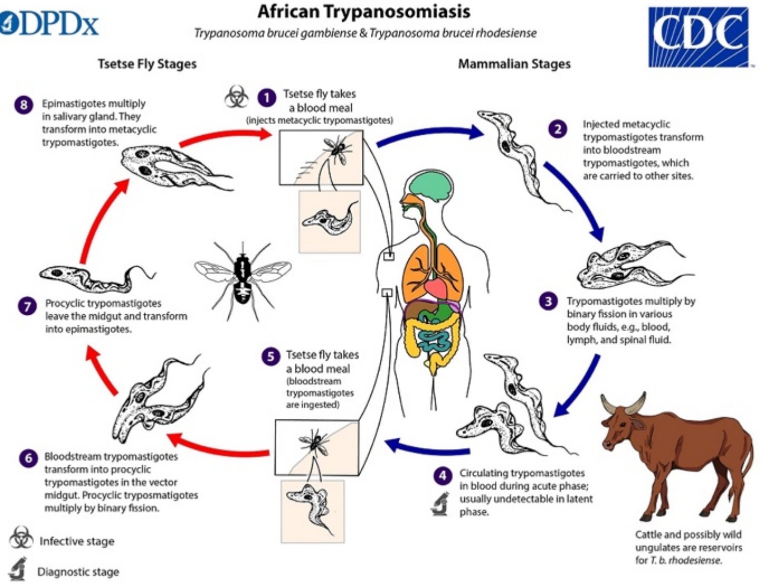

Figure 1|The lifecycle of Human African Trypanosomiasis in its vector and host[6]

Current treatments against Human African Trypanosomiasis

In 2022, the Democratic Republic of the Congo alone reported 516 cases of HAT[7], yet there is still little research and funding being invested into this NTD. Although the WHO has a new roadmap for 2021-2030 with the aim of a world free of NTDs by 2030[8], there are still only a few treatment options on the market. NTDs account for 11% of the global disease burden, but only 4% of treatments developed between 2000 and 2011 targeted these diseases[9]. Additionally, the treatments available are difficult to administer (mostly by injection), have severe side effects that could even be lethal, are expensive and have experienced emerging resistance[9]. For example, one of the drugs formerly used against *T. b. rhodesiense* is Melarsoprol (**5**), which is an arsenical with a 10% mortality rate[2]. Other drugs such as Eflornithine (**2**), effective against *T. b. gambiense*, have a complex intravenous administration[5]. Additionally, Eflornithine was originally developed for cancer therapy before being discovered as a potential medicine to treat HAT[10]. Late-stage treatment of HAT proves especially difficult as the blood-brain barrier has been crossed and thus the drugs become more toxic and complicated to administer. Other current treatment options include Pentamidine (**1**), a combination therapy between Eflornithine (**2**) and Nifurtimox (**3**), Suramin (**4**) and Fexinidazole (**6**)[5,10] (Figure 2).

	T. b. gambiense	*T. b. rhodesiense*
Early stage	**1 Pentamidine**	**4 Suramin**
Late stage	**2 Eflornithine** + **3 Nifurtimox**	**5 Melarsoprol**
Both stages	**6 Fexinidazole**	

Figure 2|Treatment of HAT[5,10]

Importance of developing new drugs

As previously discussed, current treatments of NTDs are difficult to administer, often requiring intravenous or intramuscular injections over several weeks, demanding healthcare resources and trained personnel. In addition, some drugs are outdated and have severe side effects, while the pathogen is acquiring increased drug resistance[9]. As most NTDs affect people in rural areas, lacking clean sanitary conditions, the diseases often spread rapidly, whilst seldom being detected at an early stage due to poor healthcare systems. Thus, novel medicines that are safer and easier to administer are a necessity.

The Drugs for Neglected Disease initiative (DNDi) outlined criteria for novel compounds. These criteria are followed by the novel compounds developed by the Florence group, in which this

research project took place. These include a clinical efficacy of > 95%, safe use during pregnancy and breast-feeding, < 0.1% drug related mortality, < 7 days of oral treatment (once daily), < 30€ per course of drug cost to be paid by donor agencies, and stable storage for more than 3 years in climate zone 4[11,12].

Drug discovery strategies and Natural products in drug discovery

The two main approaches for drug discovery for neglected tropical diseases are phenotypic screening and target-based screening methods[13]. Phenotypic screening includes the identification of hit molecules by screening compound libraries against whole cells (or organisms). These hit molecules are then modified to optimize the structure-activity relationship (SAR), before using the chemical proteomics method to identify the target[13,14]. Target-based screening requires the validation of a specific protein chosen as a drug target, before designing a compound that acts selectively and effectively against the chosen protein target[13,14]. Both approaches have advantages and disadvantages. Phenotypic screening is particularly useful when the molecular mechanism of action is not fully understood, as the assays do not require this information. In addition, an effective translation of the activity of these assays into a therapeutic use of the disease is more effective compared to target-based assays. However, when lacking the knowledge about the molecular mechanism of action, it often proves challenging to optimize the molecular properties of a potential drug. Additionally, phenotypic screening assays reach a considerably lower throughput than target-based assays[14]. These have the advantage of applying small-molecule screening strategies and biologic-based approaches. The molecular and chemical knowledge to investigate specific molecular hypotheses can also be used, however the molecule developed from this is sometimes irrelevant to the disease pathogenesis or provides an insufficient therapeutic index[14].

Between 1981 and 2014, 49% of new drugs were natural products or structural derivatives thereof[9], indicating a high potential for drug discovery and development. The secondary metabolites produced by living organisms, providing an evolutionary benefit, are defined as natural products. Since these secondary metabolites are often produced by various

biosynthetic pathways, they have lower hydrophobicity and a higher stereochemical content compared to purely synthetic compounds[9].

Project Aim

The aim of this project is to investigate the effect of introducing a modification into the lead compound **7** (Figure 3), that previously showed a wide-range activity against Trypanosoma parasites. This will allow a deeper understanding into the structure-activity relationship. Several compounds will be synthesised with a variation of the "R-group" seen in Figure 4, with the aim to optimise the activity and selectivity of the lead compound against *T. brucei*.

Figure 3|Lead compound **7**

Figure 4|General compound with "R-group" that will be chemically varied

Synthesis

Synthesis Scheme

Figure 5 shows the general synthesis scheme that was followed.

MsCl, Et_3N

8A

NaN_3

PPh_3

9

8B

EDCI
HOBt
DIPEA

Na_2CO_3, $Pd(PPh_3)_4$

Figure 5|General Synthesis Scheme

Methodology

3-bromophenethyl methanesulfonate 8A

Methanesulfonyl chloride (1.2 eq, 2051 mg, 17.9 mmol) and triethylamine (1.5 eq, 2265 mg, 22.38 mmol) were added to a solution of 2-(3-bromophenyl)-1-ethanol (1 eq, 3000 mg, 14.92 mmol) in dry DCM at 0 °C and stirred for 30 mins. After the reaction was confirmed by TCL to be completed, the mixture was quenched with water, extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The product

(3783 mg, 91%) was afforded as a colourless oil and directly used for the next step without purification.

Rf 0.52 (30% EtOAc/Hexane)

1-(2-azidoethyl)-3-bromobenzene 8B

The crude material **8A** was dissolved in DMF and sodium azide (3 eq, 2910 mg, 65.01 mmol) was added. The reaction mixture was heated to 85 °C and stirred overnight. After the reaction was confirmed by TLC to be completed, it was quenched with water, extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The product (3063 mg, 100%) was afforded as a colourless oil and directly used for the next step without purification.

Rf 0.64 (30% EtOAc/Hexane)

2-(3-bromophenyl)ethan-1-amine 9

Triphenylphosphine (1.5 eq, 5330 mg, 20.3 mmol) was added to 1-(2-azidoethyl)-3-bromobenzene **8B** (1 eq, 3063 mg, 13.5 mmol) in dry methanol and refluxed for 2 hours at 90 °C. After the reaction was confirmed by TLC to be completed, the solvent was evaporated. Water and a few drops of HCl were added until a pH ~4 was reached. The aqueous phase was washed with EtOAc and DCM. Then sodium hydroxide was added until a pH of ~9 was reached. The solution was extracted from DCM, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The product (2710 mg, 100%) afforded was directly used for the next step without purification. A small amount of TPP oxide was mixed inside.

Rf 0.17 (30% EtOAc/Hexane)

***N*-(3-bromophenethyl)furan-2-carboxamide 10**

2-(3-bromophenyl)ethan-1-amine **9** (1 eq, 200 mg, 1.0 mmol), furan-2-carboxylic acid (1.5 eq, 168 mg, 1.5 mmol), EDCl (1.5 eq, 288 mg, 1.5 mmol) and HOBt (20 wt% water) (1.5 eq, 230 mg, 1.5 mmol) were dissolved in DCM and then DIPEA (4 eq, 517 mg, 4.0 mmol) was added and stirred. After the reaction was confirmed by TLC to be completed, the solvent was washed with HCl (1M, aq), $NaHCO_3$ (aq) and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc/Hexane) afforded the compound (125 mg, 43%) as a sticky colourless oil.

R_f 0.21 (30% EtOAc/Hexane)

***N*-(2-(4'-chloro-[1,1'-biphenyl]-3-yl)ethyl)furan-2-carboxamide 11**

N-(3-bromophenethyl)furan-2-carboxamide **10** (1 eq, 50 mg, 0.34 mmol) was dissolved in a solution of EtOH:H_2O:Toluene (3:1:1). Then 4-chlorophenylboronic acid (1.5 eq, 39.9 mg, 0.51 mmol) and sodium carbonate (3 eq, 54.1 mg, 1.02 mmol) were added, and the mixture was degassed under nitrogen for 10 mins. Then tetrakis(triphenylphosphine) palladium(0) (0.05 eq, 9.8 mg, 0.017 mmol) was added and the reaction mixture was heated to 100 °C in a sealed tube and let to stir overnight. After the reaction was confirmed by TLC to be completed, it was quenched with $NaHCO_3$ (aq.), extracted with DCM, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc/Hexane) afforded the compound (21.5 mg, 39%) as a yellow solid.

R_f 0.17 (30% EtOAc/Hexane)

_N_-(3-bromophenethyl)-2-methylfuran-3-carboxamide 12

2-(3-bromophenyl)ethan-1-amine **9** (1 eq, 100 mg, 0.50 mmol), 2-methylfuran-3-carboxylic acid (1.5 eq, 94.5 mg, 0.75 mmol), EDCl (1.5 eq, 143.7 mg, 0.75 mmol) and HOBt (20 wt% water) (1.5 eq, 114.8 mg, 0.75 mmol) were dissolved in DCM and then DIPEA (4 eq, 258.4 mg, 2.0 mmol) was added and stirred. After the reaction was confirmed by TLC to be completed, the solvent was washed with HCl (1M, aq), $NaHCO_3$ (aq) and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc/Hexane) afforded the compound (35.2 mg, 23%) as a sticky colourless oil.

$\mathbf{R_f}$ 0.36 (30% EtOAc/Hexane)

_N_-(2-(4'-chloro-[1,1'-biphenyl]-3-yl)ethyl)-2-methylfuran-3-carboxamide 13

_N_-(3-bromophenethyl)-2-methylfuran-3-carboxamide **12** (1 eq, 35.2 mg, 0.11 mmol) was dissolved in a solution of EtOH:H_2O:Toluene (3:1:1). Then 4-chlorophenylboronic acid (1.5 eq, 26.8 mg, 0.17 mmol) and sodium carbonate (3 eq, 36.3 mg, 0.34 mmol) were added, and the mixture was degassed under nitrogen for 10 mins. Then tetrakis(triphenylphosphine) palladium(0) (0.05 eq, 6.6 mg, 0.0057mmol) was added and the reaction mixture was heated to 100 °C in a sealed tube and left to stir overnight. After the reaction was confirmed by TLC to be completed, it was quenched with $NaHCO_3$ (aq.), extracted with DCM, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc/Hexane) afforded the compound (14.1 mg, 36%) as a sticky clear oil.

$\mathbf{R_f}$ 0.28 (30% EtOAc/Hexane)

***N*-(3-bromophenethyl)-2-methyloxazole-4-carboxamide 14**

2-(3-bromophenyl)ethan-1-amine **9** (1 eq, 100 mg, 0.50 mmol), 2-methyl-1,3-oxazol-4-carboxylic acid (1.5 eq, 95.3 mg, 0.75 mmol), EDCl (1.5 eq, 143.7 mg, 0.75 mmol) and HOBt (20 wt% water) (1.5 eq, 114.8 mg, 0.75 mmol) were dissolved in DCM and then DIPEA (4 eq, 258.4 mg, 2.0 mmol) was added and stirred. After the reaction was confirmed by TLC to be completed, the solvent was washed with HCl (1M, aq), $NaHCO_3$ (aq) and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc/Hexane) afforded the compound (52.6 mg, 68%) as solid white flakes.
R_f 0.1 (30% EtOAc/Hexane)

***N*-(2-(4'-chloro-[1,1'-biphenyl]-3-yl)ethyl)-2-methyloxazole-4-carboxamide 15**

N-(3-bromophenethyl)-2-methyloxazole-4-carboxamide **14** (1 eq, 50.0 mg, 0.16 mmol) was dissolved in a solution of EtOH:H_2O:Toluene (3:1:1). Then 4-chlorophenylboronic acid (1.5 eq, 37.9 mg, 0.24 mmol) and sodium carbonate (3 eq, 51.3 mg, 0.49 mmol) were added, and the mixture was degassed under nitrogen for 10 mins. Then tetrakis(triphenylphosphine) palladium(0) (0.05 eq, 9.3 mg, 0.008mmol) was added and the reaction mixture was heated to 100 °C in a sealed tube and let to stir overnight. After the reaction was confirmed by TLC to be completed, it was quenched with $NaHCO_3$ (aq.), extracted with DCM, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc/Hexane, 1% Et_3N) afforded the compound (45.5 mg, 83%) as solid white flakes.
R_f either 0.12 (30% EtOAc/Hexane, 1% Et_3N)

_N_-(3-bromophenethyl)-1-methyl-1_H_-pyrrole-2-carboxamide 16

2-(3-bromophenyl)ethan-1-amine **9** (1 eq, 100 mg, 0.50 mmol), 1-methyl-2-pyrolle carboxylic acid (1.5 eq, 93.9 mg, 0.75 mmol), EDCl (1.5 eq, 143.7 mg, 0.75 mmol) and HOBt (20 wt% water) (1.5 eq, 114.8 mg, 0.75 mmol) were dissolved in DCM and then DIPEA (4 eq, 258.4 mg, 2.0 mmol) was added and stirred. After the reaction was confirmed by TLC to be completed, the solvent was washed with NaOH (1M), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (10% EtOAc/Hexane, 1% Et_3N) afforded the compound (89 mg, 58%) as a sticky pale-yellow oil.

$\mathbf{R_f}$ 0.071 (10% EtOAc/Hexane, 1% Et_3N)

_N_-(2-(4'-chloro-[1,1'-biphenyl]-3-yl)ethyl)-1-methyl-1_H_-pyrrole-2-carboxamide 17

_N_-(3-bromophenethyl)-1-methyl-1_H_-pyrrole-2-carboxamide **16** (1 eq, 80 mg, 0.26 mmol) was dissolved in a solution of EtOH:H_2O:Toluene (3:1:1). Then 4-chlorophenylboronic acid (1.5 eq, 61.1 mg, 0.39 mmol) and sodium carbonate (3 eq, 82.8 mg, 0.78 mmol) were added, and the mixture was degassed under nitrogen for 10 mins. Then tetrakis(triphenylphosphine) palladium(0) (0.05 eq, 15.1 mg, 0.013 mmol) was added and the reaction mixture was heated to 100 °C in a sealed tube and let to stir overnight. After the reaction was confirmed by TLC to be completed, it was quenched with $NaHCO_3$ (aq.), extracted with DCM, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc/Hexane, 1% Et_3N) afforded the compound (74.6 mg, 85%) as a sticky brown oil.

$\mathbf{R_f}$ 0.1 (30% EtOAc/Hexane, 1% Et_3N)

2-amino-*N*-(3-bromophenethyl)thiazole-4-carboxamide 18

2-(3-bromophenyl)ethan-1-amine **9** (1 eq, 100 mg, 0.50 mmol), 2-aminothiazole-4-carboxylic acid (1.5 eq, 108.1 mg, 0.75 mmol), EDCl (1.5 eq, 143.7 mg, 0.75 mmol) and HOBt (20 wt% water) (1.5 eq, 114.8 mg, 0.75 mmol) were dissolved in DCM and then DIPEA (4 eq, 258.4 mg, 2.0 mmol) was added and stirred. After the reaction was confirmed by TLC to be completed, the solvent was washed with HCl (1M, aq) and $NaHCO_3$ (aq). Sodium hydroxide was added to the aqueous layer until a pH of ~9 was reached, and the product was extracted with DCM, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The product (80.7 mg, 49%) was afforded as a sticky dark yellow oil and directly used for the next step without purification.

R_f 0.13 (30% EtOAc/Hexane)

2-amino-*N*-(2-(4'-chloro-[1,1'-biphenyl]-3-yl)ethyl)thiazole-4-carboxamide 19

2-amino-*N*-(3-bromophenethyl)thiazole-4-carboxamide **18** (1 eq, 80 mg, 0.25 mmol) was dissolved in a solution of EtOH:H_2O:Toluene (3:1:1). Then 4-chlorophenylboronic acid (1.5 eq, 57.5 mg, 0.37 mmol) and sodium carbonate (3 eq, 78.0 mg, 0.74 mmol) were added, and the mixture was degassed under nitrogen for 10 mins. Then tetrakis(triphenylphosphine) palladium(0) (0.05 eq, 14.2 mg, 0.012 mmol) was added and the reaction mixture was heated to 100 °C in a sealed tube and let to stir overnight. After the reaction was confirmed by TLC to be completed, it was quenched with $NaHCO_3$ (aq.), extracted with DCM, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (50% EtOAc/Hexane, 1% Et_3N) afforded the compound (24.3 mg, 28%) as a sticky yellow oil.

R_f 0.19 (50% EtOAc/Hexane, 1% Et_3N)

Results and Discussion

A total of five final compounds were synthesised (^{1}H NMR data in supplementary information). Due to time constraints, the compounds synthesised were not biologically tested for their trypanocidal activity in this research project. A pure sample of compound **11** was synthesised, allowing for biological testing in future projects. A suitable methodology was chosen for synthesis of compound **11**, as reflected in the purity of the sample obtained.

Analysis of compound **13** by ^{1}H NMR shows a triplet at ~2.90 ppm indicative of a debromination by-product. Additionally, only 17 hydrogens are present on the ^{1}H NMR spectrum obtained for compound **13**, instead of the 18 hydrogens that are expected for correct product formation, thus indicating that an unwanted side reaction occurred. Another by-product produced in the final step Suzuki-Miyaura coupling reaction that converts compound **12** to **13** is visible through the multiplet at ~6.79 ppm. Interestingly, compounds **15**, **17**, and **19** show the same unknown by-product at ~6.79 ppm, indicating that the synthetic route chosen (as seen in Figure 5) is not suitable for the heterocycles that were added in these compounds. All heterocycles added in these compounds contain either a nitrogen or an additional methyl group, unlike lead compound **7** and compound **11**, which might be linked to the unknown by-product formed. Analysis of compound **19** also indicates the presence of triphenylphosphine oxide mixed into the compound.

In order to eliminate the by-products, present in compounds **13**, **15**, **17** and **19**, the synthetic route chosen must be optimised. For example, by conducting the Suzuki-Miyaura coupling before the amide coupling (Figure 6). Alternatively, one could start the synthesis with a Suzuki-Miyaura coupling between the alcohol (2-(3-bromophenyl)-1-ethanol) and 4-chlorophenylboronic acid (Figure 7).

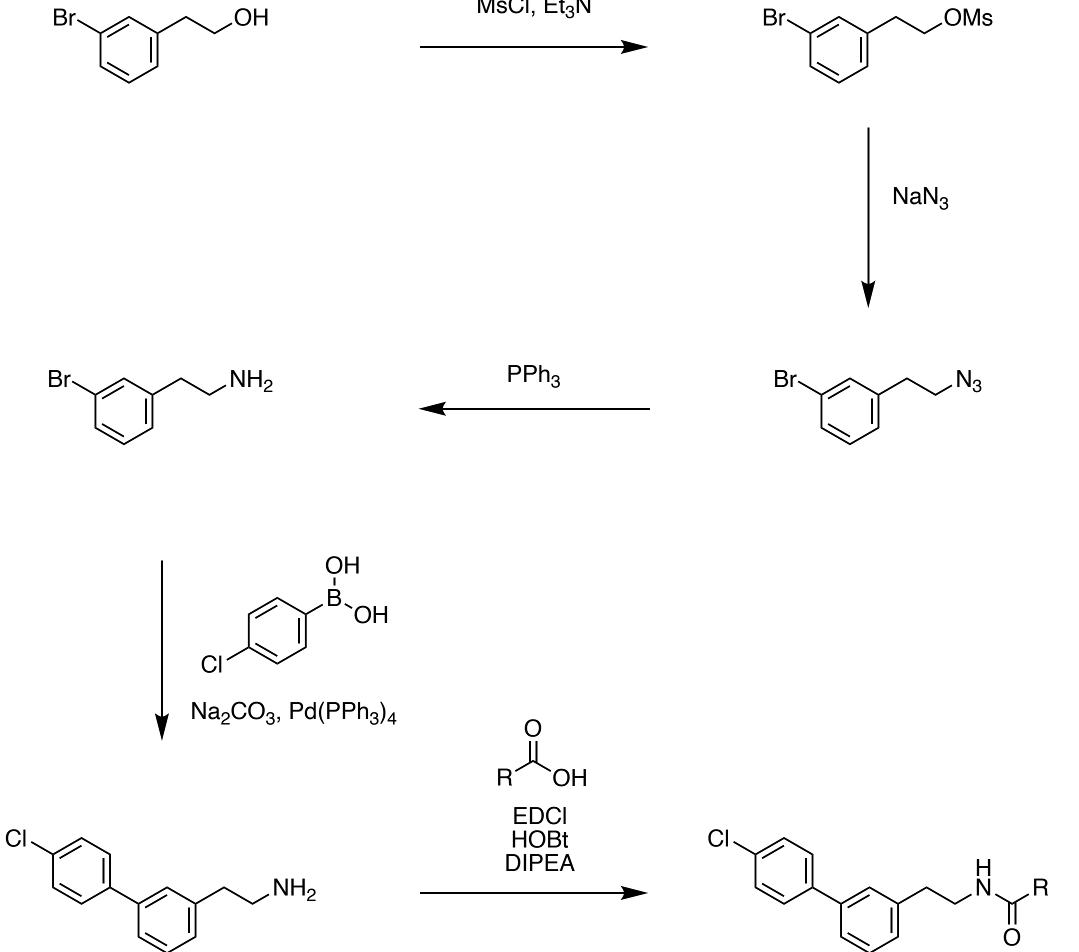

Figure 6|Possible synthetic route that introduces the additional aromatic ring first, followed by the amide coupling reaction

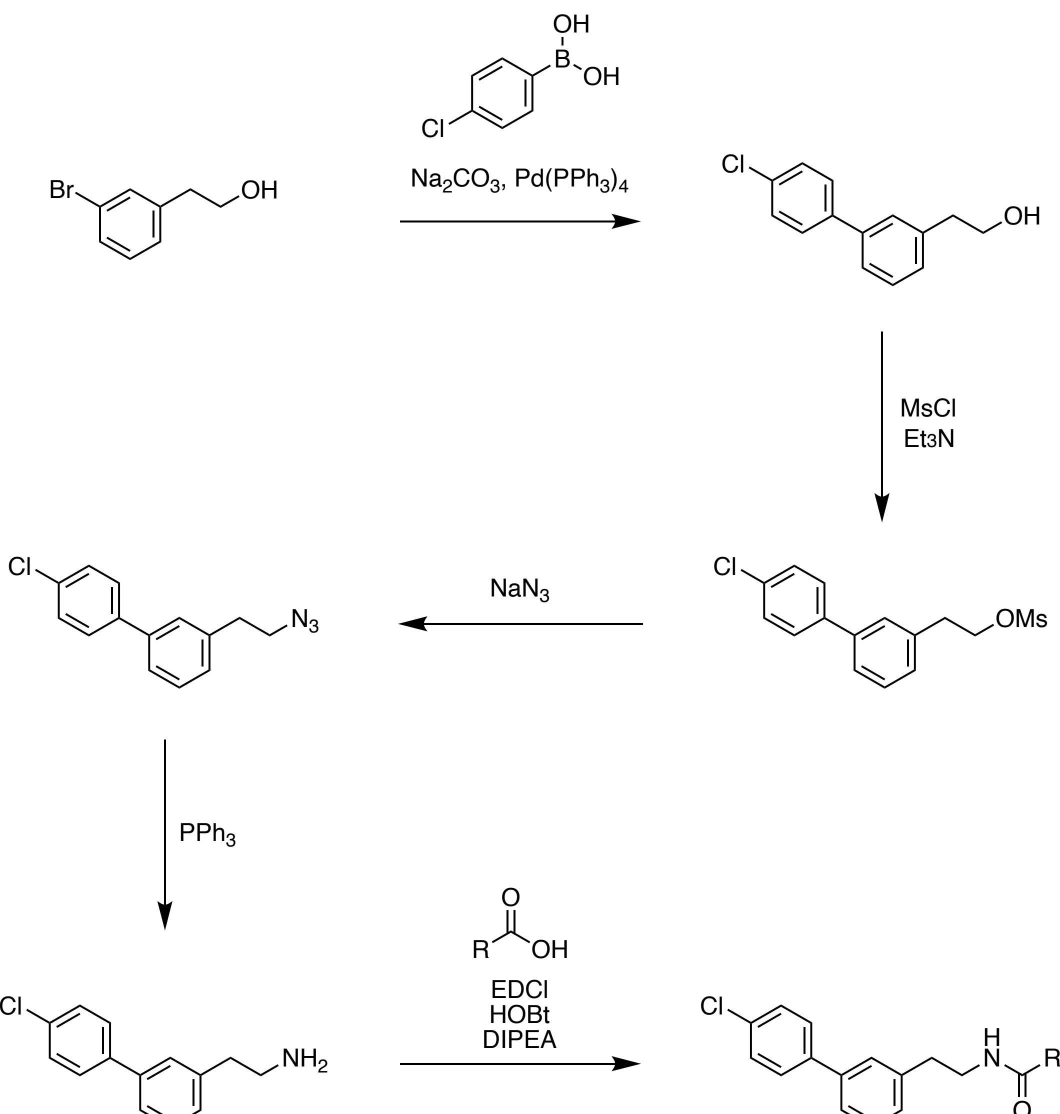

Figure 7|Possible synthetic route beginning with Suzuki-Miyaura coupling to 2-(3-bromophenyl)-1-ethanol

Future Work

In this project, five final compounds were synthesised. Time constraints prohibited the compounds from being biologically tested for their trypanocidal activity. Additionally, four of the synthesised compounds were not pure enough to be used for biological testing. Thus, future work includes experimenting with different synthetic routes, like those suggested above. Once pure products are synthesised, biological testing should occur to evaluate the trypanocidal activity of the compounds. Additionally, the compounds should be tested for their toxicity against Hela cells, thus testing their selectivity. If the biological tests yield a positive result, meaning a compound showing high activity and high selectivity, then this

should be further investigated, in particular to understand its mode of action, allowing further progress towards a development of a suitable treatment option for HAT.

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Supplementary Information

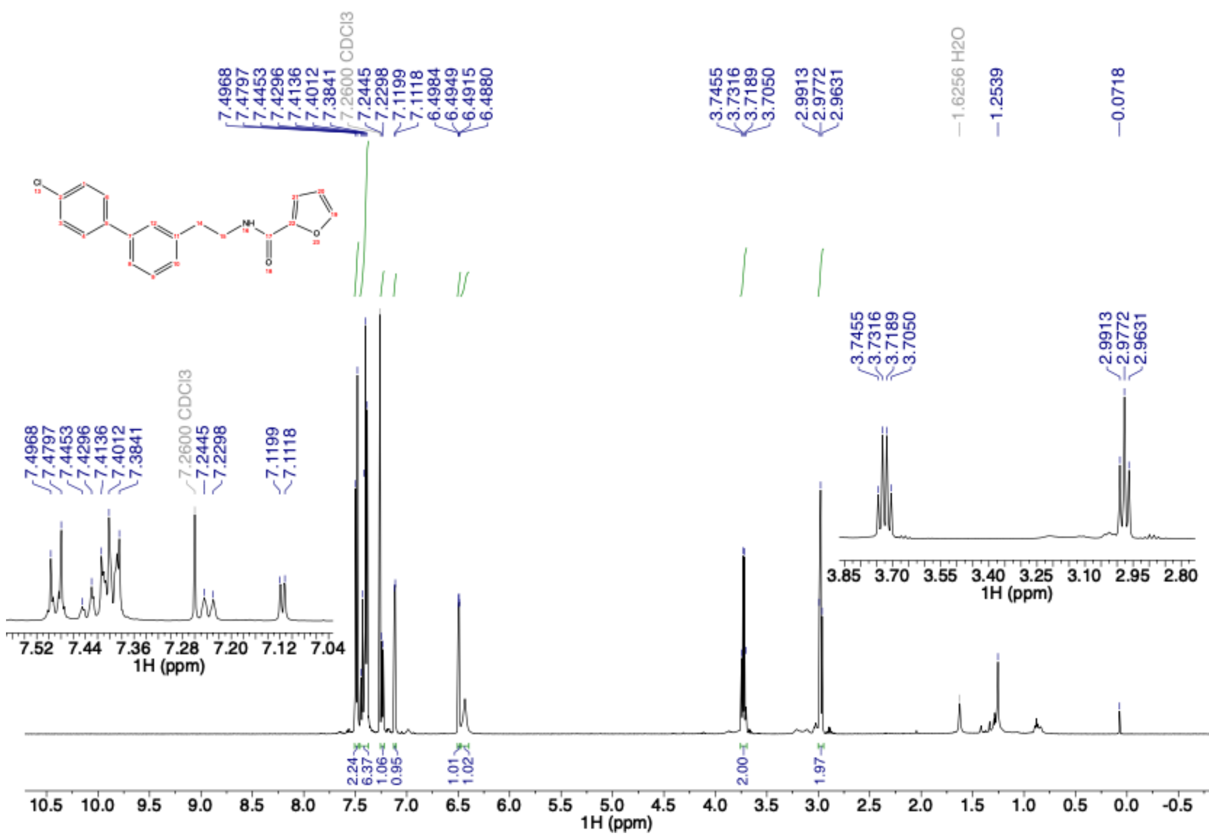
General

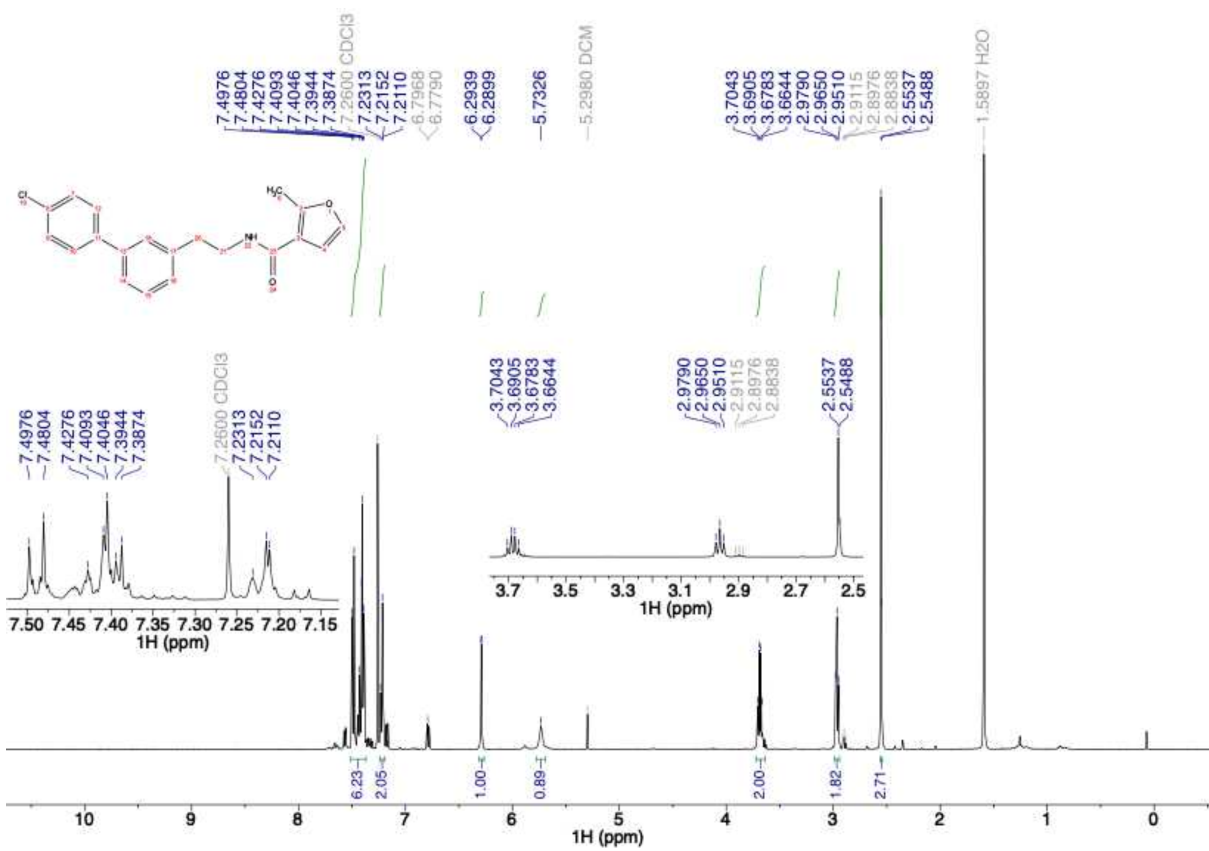
^{1}H NMR data was recorded on a Bruker Avance II 400 (400.1 MHz), Bruker Avance III-HD 500 (499.9 MHz), and Bruker Avance III 500 (500.1 MHz). Deuterated solvents (chloroform-d 7.26 ppm) were used as a reference. The chemical shifts are reported in parts per million (ppm) on a delta (δ) scale.

Analytical Thin Layer Chromatography (TLC) was carried out on pre-coated (25 μm) Merck Kieselger 60 F254 plates that were visualised by ultraviolet (UV) light at 254 nm.

Flash Column Chromatography was carried out on Merck silica gel 60 (40-63 μm) under positive pressure of compressed air. Reagent-grade solvent were used as purchased.

^{1}H NMR Data

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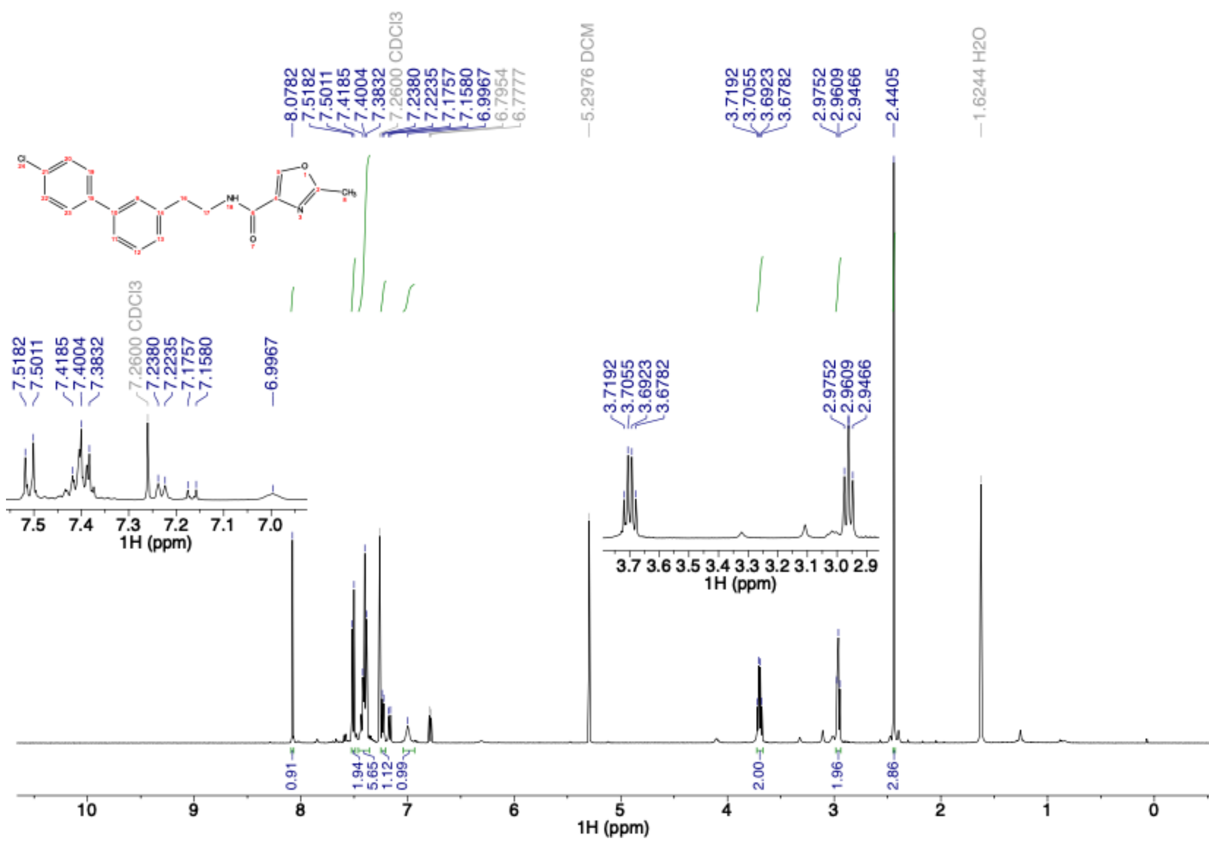
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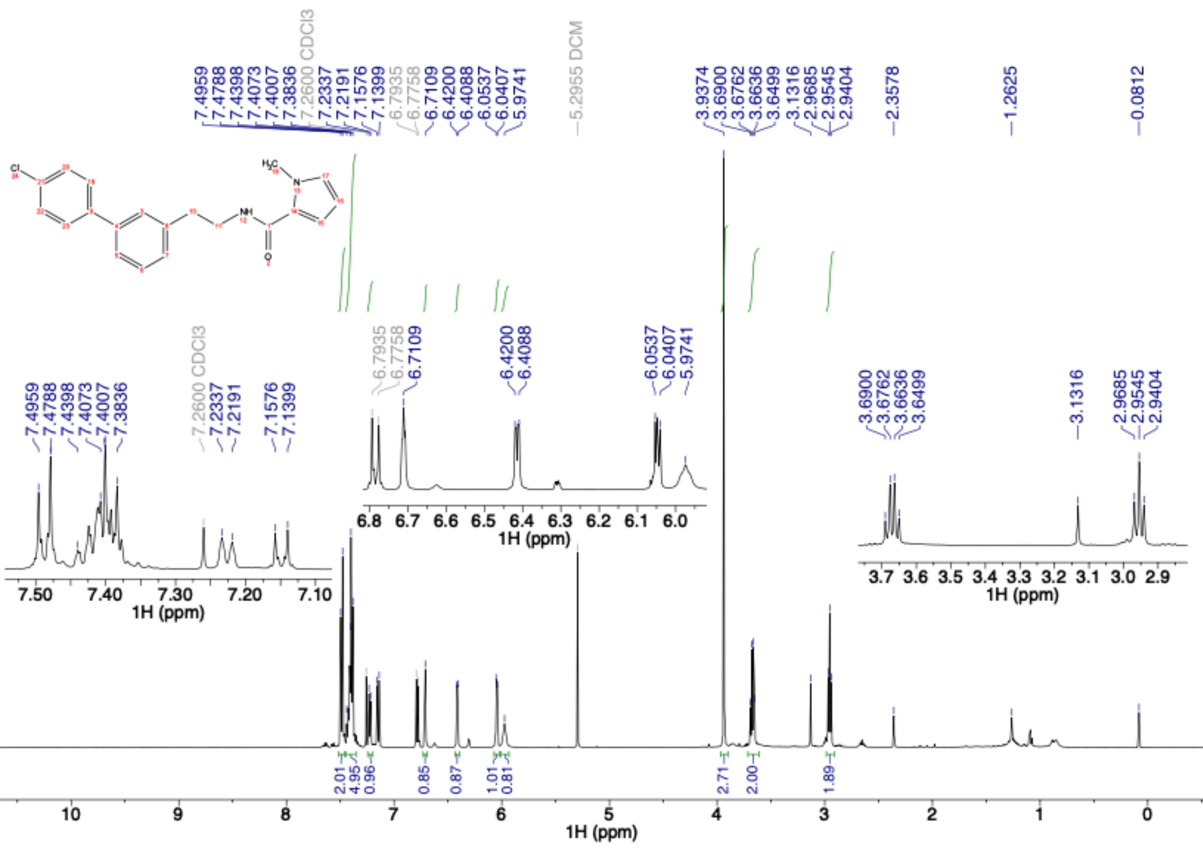
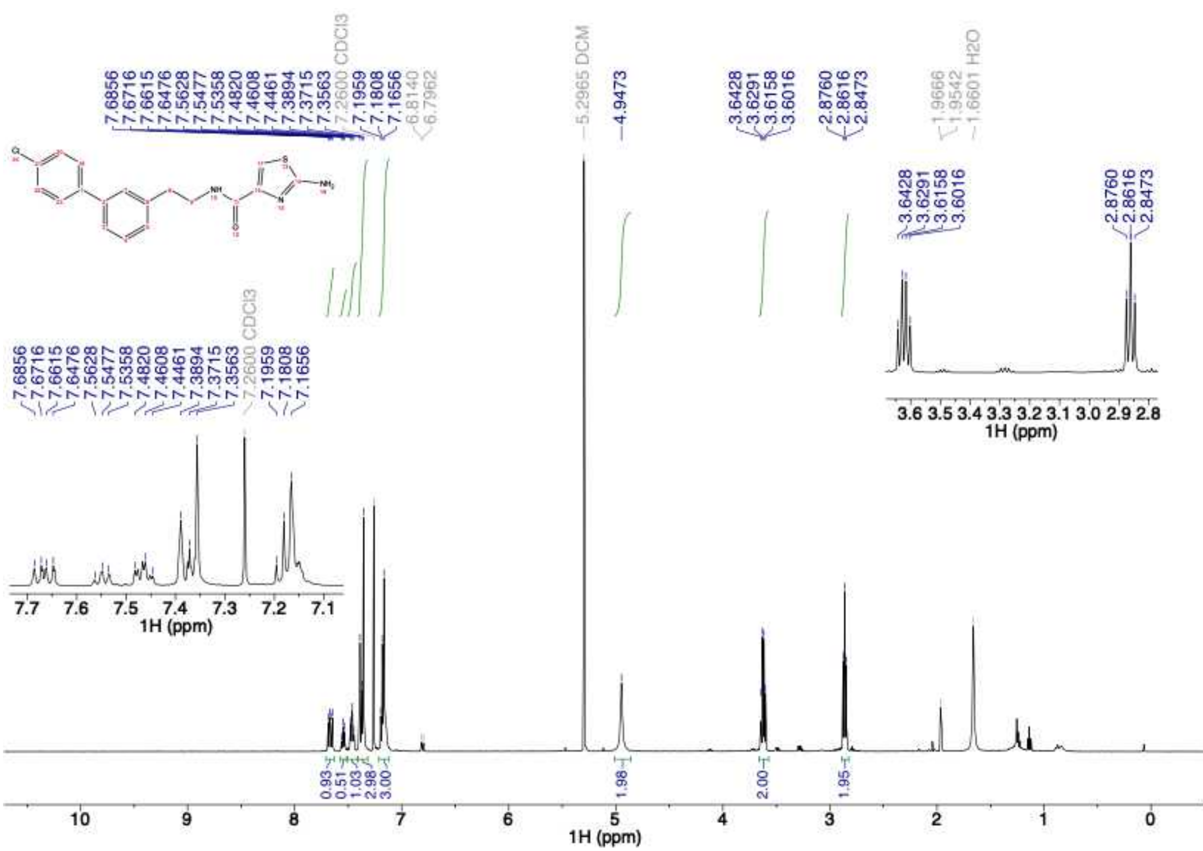
1H (ppm)

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7.6615
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7.5628
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7.5358
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7.4461
7.3894
7.3715
7.3563
7.2600 CDCl3
7.1959
7.1808
7.1656
6.8140
6.7962
5.2965 DCM
4.9473
3.6428
3.6291
3.6158
3.6016
2.8760
2.8616
2.8473
1.9666
1.9542
1.6601 H2O
0.93
0.51
1.03
2.98
3.00
1.98
2.00
1.95
1H (ppm)