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N^1,N^1-Dimethyl-N^3-(3-(trifluoromethyl)phenethyl)propane-1,3-diamine, a new lead for the treatment of human African trypanosomiasis☆

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ABSTRACT

The natural product, convolutamine I (**1**), has anti-trypanosomal activity however it has a high molecular weight of 473 due to a presence of 3 bromine atoms. The synthesis of the natural product convolutamine I (**1**) together with its analogues are presented. A SAR study against *Trypanosoma brucei brucei* led to compounds with improved physico-chemical properties: lower molecular weight and lower log *P* while maintaining potency (with a slight 2-fold improvement).

1. Introduction

Human African trypanosomiasis, also known as African sleeping sickness, is endemic in the regions of sub-Saharan Africa, affecting around 70 million people in 36 countries [1]. The disease is caused by protozoa of the species *Trypanosoma brucei* and transmitted through the bite of an infected tsetse fly or passed from mother to child as the parasite can pass the placenta and infect the foetus. At the early stage, the trypanosomes multiply in subcutaneous tissues, blood and lymph and patients develop insignificant symptoms such as fever, headaches, joint pains and itching. In time, the parasites cross the blood–brain barrier and infect the central nervous system and patients start to develop confusion, sensory disturbances, poor coordination and sleep cycle disturbance. Without treatment, African sleeping sickness is fatal [1]. Current treatment for the neurological stage includes melarsoprol, an arsenical derivative known to have many undesirable or fatal (3–10%) side effects, resistance is developing and there is a failure rate of up to 30% [2]; eflornithine which is less toxic, has compliance issues and is only effective against the *Trypanosoma brucei gambiense* subspecies [3]; or a combination treatment of nifurtimox and eflornithine which is less toxic but not effective against the *Trypanosoma brucei rhodesiense* subspecies [1]. New, safe and effective drugs are urgently needed. As part of a continuing study for novel entities with high efficacy and less toxicity for human African trypanosomiasis, we have previously described the active natural product, convolutamine I (**1**), isolated from the bryozoan *Amathia tortusa* [4]. In order for a new drug to combat human African trypanosomiasis at the late stage of the disease, the active drug should be able to pass blood–brain barrier. Analyses of central nervous system (CNS) drugs [5,6] showed CNS drugs have molecular weight (MW) in the range from 141 to 452, clogP from −0.66 to 6.1 and topological polar surface area (tPSA) from 3.2 to 97 Å^2. Combined analyses of CNS drugs and drug candidates have provided guidelines on these physico-chemical properties [5,6], such as $250 < MW < 355$, $1.5 < clogP < 2.7$, and $25 < tPSA < 60$. In this paper we present a synthetic route to convolutamine I (**1**) and a series of analogues designed to lower MW, clogP and keep tPSA in the CNS drug range while maintaining activity.

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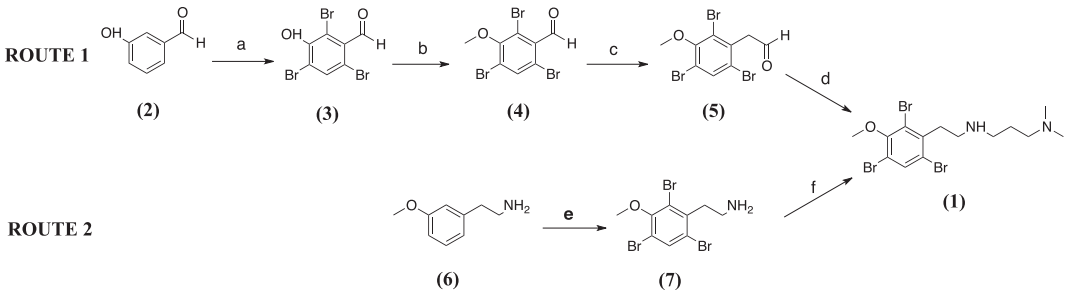

Scheme 1. Synthesis of **1**. Reagent and conditions: (a) Br_2, H_2O, rt, 3 days, 65% yield; (b) MeI, K_2CO_3, DMF, rt, 65% yield; (c) (i) $ClCH_2COOEt$, NaOEt, dry toluene, (ii) NaOH 30%, (iii) HCl con., reflux, 13% yield; (d) $NH_2(CH_2)_3NMe_2$, $NaBH_4$/K10, microwave, 10 min, 56% yield, (e) Br_2, AcOH/HCl, 80 °C, 85% yield; (f) 3-chloro-*N*,*N*-dimethylpropan-1-amine, H_2O/CH_2Cl_2, 140 °C, 10 min, 60% yield.

2. Results and discussion

2.1. Chemistry

Convolutamine I (**1**) was synthesized by two different routes in order to facilitate analogue development. In the first route, 3-hydroxybenzaldehyde (**2**) was brominated [7] to give the brominated aldehyde (**3**) that was then treated with methyl iodide in DMF in the presence of K_2CO_3 to give the methoxy brominated benzaldehyde (**4**). Carbon–carbon elongation of **4** was performed *via* Darzens condensation to give **5** which was subsequently condensed with N^1,N^1-dimethylpropane-1,3-diamine in the presence of mixture of $NaBH_4$ and clay K10 under microwave irradiation [8] to give **1** (Route 1, Scheme 1).

In the second synthetic route, 3-methoxy phenylethanamine (**6**) was brominated in the presence of bromine in acetic acid to give the 2-,4-,6-tribromo derivative (**7**). A dimethylaminoethyl side chain was introduced to **7** by an N-alkylation reaction [9] with alkyl chloride to give convolutamine I (**1**) (Route 2, Scheme 1). NMR data of **1** was consistent with the isolated natural product [4].

Analogues **8**, **9**, **12**, **13**, **17**, **18** with a one carbon shorter chain between the phenyl group and the first nitrogen compared to **1** were synthesized by brominating 3-hydroxybenzaldehyde or 4-hydroxybenzaldehyde and condensation with N^1,N^1-dimethylpropane-1,3-diamine according to Scheme 2. Compounds **19**–**22** (Table 1) were synthesized in an analogous route without the bromination step. The carbon NMR data for this series with 11 distinct signals confirmed one carbon shorter in the side chain of these analogues. Compounds **8** and **9** had (+)-LRESIMS 1:3:3:1 cluster of ions indicative of 3 bromine atoms. **8** and **9** had one aromatic proton signal at δ_H 7.60 and 7.96, respectively, and three upfield quaternary carbon signals at 105–120 ppm, confirming a three-bromine-substituted aromatic ring. Compounds **12** and **13** had two singlet aromatic protons *para* to each other at δ_H 7.53, 6.86 and 7.73, 7.21, respectively, and two diagnostic quaternary brominated carbon signals at δ_C 105–120, confirming a 2,4-dibromo substituted aromatic ring. Compound **18** had one aromatic signal at δ_H 7.63 assigned to 2 eq. protons; its attached carbon had a chemical shift of δ_C 133.8, confirming a 2,5-dibromo-4-methoxy substituted aromatic ring.

Analogues with 2 bromine substituents (**25**, **26**) or no bromine (**29**) were synthesized following the reaction sequence of Scheme 2. To achieve a 2 bromine-substituted phenethylamine, a less acidic condition and a lower reaction temperature (60 °C) were used (Scheme 3). The intermediates **23** and **24** were used as a mixture in the N-alkylation step. The mixture of products **25** and **26** was purified and separated by reversed-phase HPLC. All final compounds and intermediates were fully characterized by the usual spectroscopic methods (see Experimental section). The (+)-LRESIMS of **25** revealed a 1:3:1 cluster of ions at *m*/*z* 393/395/397 $[M + H]^+$, indicative of two bromine atoms. The ^1H NMR spectrum of **25** shows two aromatic protons at δ_H 7.65 (s, 1H) and 6.78 (s, 1H), a methoxyl signal at 3.84 (s, 3H), a triplet–pentet–triplet pattern for the 1,3-disubstituted propane unit (NHR–CH_2–CH_2–CH_2–N(Me)$_2$) at δ_H 2.27 (t, J = 7.2 Hz, 2H), 1.65 (p, J = 7.1 Hz, 2H) and 2.67 (t, J = 7.1 Hz, 2H), a four proton multiplet for the di-substituted ethane unit at δ_H 2.84–2.86 (m, 4H), and an N-methyl signal for 2 eq. methyl groups at δ_H 2.17 (6H, s). The g-COSY correlations confirm the assignment of the δ_H 2.27, 1.65, 2.67 to the NHR–CH_2–CH_2–CH_2–N$(CH_3)_2$ substructure. The HSQC allows the assignment of all protons to their directly attached carbons, confirming one aromatic proton flanked by two bromine atoms with a downfield proton chemical shift (δ_H 7.65) and a downfield carbon chemical shift for its attached carbon (δ_C 136.2). The structure elucidation for **25** is completed with HMBC correlations of the 2 eq. N-methyl groups at δ_H 2.17 (s, 6H) to the terminal carbon (δ_C 58.0) of the propane unit (NHR–CH_2–CH_2–**C**H_2–N$(CH_3)_2$), the proton of propane unit (δ_H 2.67) to the second carbon (δ_C 49.4) of the ethane unit and the proton of the ethane unit (δ_H 2.86) to carbons (δ_C 139.9, 115.0 and 113.9) of the aromatic ring. Compound **26** was distinguished from **25** by the two aromatic proton signals at δ_H 7.47 and 6.67 with a typical coupling constant of 8.8 Hz for two adjacent aromatic protons. The carbon bearing the proton δ_H 6.67 had the chemical shift of δ_C 111.2, confirming its position being adjacent to the methoxy bearing carbon and 2,6-dibromo substitutions in the aromatic ring.

The alkylation reactions were first performed in NaH/DMF or THF, however this led to multi-alkylated products rather than mono-alkylated products. Milder basic conditions such as triethylamine in chloroform/ethanol [10], or $NaHCO_3$, SDS in water at 80 °C [11], or Cs_2CO_3 in DMF at rt [12], failed to produce products. In the past few years, microwave assisted reactions have been employed and have successfully delivered high yield, clean products with short reaction times. The efficiency of microwave irradiation over the conventional thermal process lies in its uniform heat delivery to all reactants in a closed reaction vessel. Monitored with LC–UV–MS for the formation of convolutamine I (**1**), the N-alkylation reaction gave the best yield in water/chloroform at 70:30 or 90:10 ratio depending on water solubility of reagents, at pH10 using sodium hydroxide 2 M, and a microwave temperature at 140 °C for 10 min. We also found that product yield was the same if we used sodium hydroxide or triethylamine for pH adjustment, however the partition purification step was more efficient if sodium hydroxide was used. Under these optimized conditions, mono-alkylated and di-alkylated products were obtained in a ratio of 2:1 or 3:1 (mono-alkylation:di-alkylation) while tri-alkylated amines were not formed as monitored by LC–UV–MS. If the reaction temperature was increased to 150 °C or 160 °C, the percentage of di-alkylated product was also increased.