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A synthesis of tiruchanduramine and a reinvestigation of its glycosidase inhibitory activity

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ABSTRACT

Tiruchanduramine **1** was prepared using a convergent strategy with the longest linear sequence being eight steps. Synthetic **1**, displayed a broader range of inhibition than reported previously and, in addition to α-glucosidases, **1** also inhibits almond β-glucosidase, β-galactosidase and β-*N*-acetylglucosaminidase from jack bean.

1. Introduction

The alkaloid tiruchanduramine **1** (Fig. 1.) was isolated by Ravinder et al.[1] from the ascidian *Synoicum macroglossum* and was shown to consist of a β-carboline core, substituted with a side chain which contains a cyclic 5-membered guanidine. Tiruchanduramine **1** was found to be a potent α-glucosidase inhibitor[2] when compared with acarbose, a drug commonly used to treat type 2 diabetes with an IC_{50} of 100 μg/mL compared with tiruchanduramine 78.2 μg/mL.

Ravinder et al.[1] also reported the synthesis of the natural product in racemic form over 10 steps in 3.2% overall yield from tryptophan and but-3-en-1-ol. Their linear strategy began with the β-carboline-3-carboxylic acid **2**,[3] easily prepared in 4 steps from tryptophan, which was coupled with the amine **3**, prepared in 5 steps from but-3-en-1-ol, to give the amide **4**. This was converted into the hydrochloride salt of **1** via a 4-step protocol involving the introduction of the guanidine under Mitsunobu conditions (Scheme 1). In our synthesis it was hoped to adopt a more convergent approach in which the guanidine heterocycle **5** is prepared separately then coupled to the β-carboline-3-carboxylic acid **2**.

2. Discussion

Initial attempts at the synthesis of **5** began with the Cbz-protection of 3-aminopropan-1-ol **6** to give **7** in 88% yield[4] which was oxidized to the aldehyde **8** using PCC in 60% yield.[5] The nitro-aldol reaction of **8** with nitromethane catalysed by DIPEA gave **9** in 90% yield. Reduction of **9** with nickel boride and sodium borohydride gave an intermediate amine which was guanidinylated *in situ* with **10** to give the guanidine **11** in 81%. Cyclisation of **11** was effected under conditions similar to those previously employed in our work on cylindrospermopsin.[6,7] Thus treatment of **9** with a combination of triphenylphosphine, iodine and imidazole at −20 °C resulted in the complete disappearance of the starting material and the formation of **12** as indicated by ^{1}H NMR (Scheme 2).

Attempted purification of **12** was difficult as the product co-eluted with triphenylphosphine oxide and was also unstable to silica gel as had been previously observed with similar structures.[8] We thus switched to using dppe as a substitute for triphenylphosphine and found that the cyclisation reaction proceeded in a similar fashion. Purification of **12** was easily achieved in high yield

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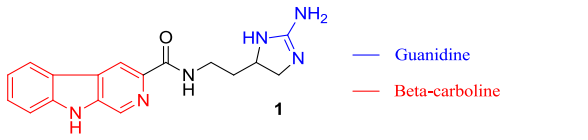
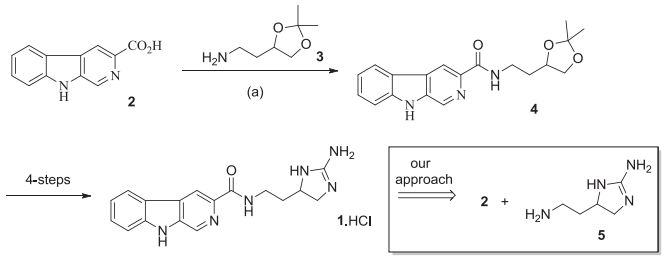
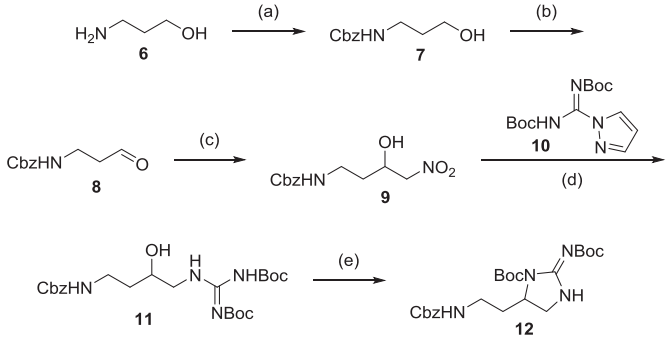


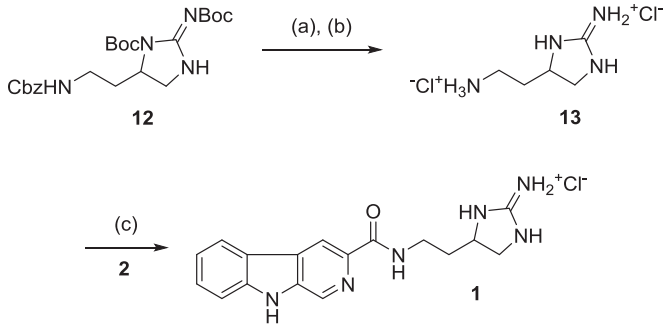
Fig. 1. Structure of tiruchanduramine (1).



Scheme 1. Ravinder's synthesis of **1** (a) DCC, DMAP, CH_2Cl_2, 62%, or (EDCI, HOBT, DMF) 65%.



Scheme 2. Synthesis of guanidine **11** (a) CbzCl, NaOH, 0 °C, 18 h, 88%. (b) PCC, CH_2Cl_2, 5 h, 60%. (c) Nitromethane, DIPEA, CH_2Cl_2, 5 days, 90%. (d) i) $Ni(II)Cl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 4 h. ii) **10** (1.2 equiv.), NEt_3, 3 days, 81%. (e) Dppe, imidazole, I_2, CH_2Cl_2, −20 °C, 2 h, quantitative.



Scheme 3. Synthesis of tiruchanduramine **1**. (a) Pd/C 10%, MeOH. 24 h. (b) HCl (3 M), 24 h. (c) i) **2**, CDI, THF:DMF (1:1), ii) **13**, NEt_3, 1 week, 11.5%.

and good purity (>95%) by trituration/precipitation of the crude reaction product with diethyl ether. With **12** in hand we next attempted to selectively deprotect the terminal amine under hydrogenation conditions and thus treated it with H_2 over Pd/C. This resulted in the loss of the Cbz−protecting group, however it was apparent from ^{1}H NMR analysis that a mixture of products had been formed. This mixture might possibly have arisen from the intermediate amine undergoing protecting group migration as has been observed previously in related systems.[8] We thus took this mixture and removed the Boc-protecting groups by treatment with aqueous 3 M HCl to give the crude guanidine **13** as it's dihydrochloride salt. The coupling of **13** with the acid **2** proved capricious but was eventually achieved by treatment of **2** with 1,1′-carbonyldiimidazole (CDI) in a 1:1 mixture of THF and DMF[9] followed by addition of the free base of **13**. After purification by HPLC, tiruchanduramine **1** was obtained as its hydrochloride salt in 11.5% yield over three steps (see Scheme 3).

Our compound gave identical data to those reported in the literature[1] with the exception of one aromatic CH signal in the ^{1}H NMR, which was reported at δ 8.20 (1H, d, J 8.0 Hz) ppm that we observed at δ 8.37 (1H, d, J 7.8 Hz) ppm. We were unable to obtain an original sample of **1** or copies of original NMR spectra.

3. Assays

Synthetic **1**, the known carboxylic acid **2** and the guanidine **13** were submitted to assays on a panel of glycosidases at 143 μg/mL and **1** was more inhibitory (over 50%) to Bacillus α-glucosidase than **2** (31%) and **13** (11%). Compound **1** was also more inhibitory to yeast α-glucosidase (26%) than **2** (9%) and **13** gave no inhibition. Synthetic **1** gave over 40% inhibition of β-glucosidase whereas **2** was a much weak inhibitor (14%). Heterocycle **2** was not inhibitory to jack bean hexosaminidase but **1** gave 37% inhibition. Both **1** (20%) and **2** (37%) inhibited bovine hexosaminidase. β-Galactosidase was strongly inhibited (80%) by **1** but **2** and **13** were not inhibitory to this enzyme. Compound **13** in fact weakly increased the activity of the bovine (11%) and jack bean (15%) hexosaminidases at the top concentration used. α-Galactosidase and α-mannosidase were not inhibited by any of the compounds. Our results confirm the α-glucosidase inhibition reported by Ravinder[1] although the compound is only a weak to moderate inhibitor of the two α-glucosidases tested here. It should be noted that acarbose used as the comparator for **1** by Ravinder is not a particularly potent inhibitor of glucosidases.[1] Compound **1** does, however, show a broad range of inhibition and also inhibits almond β-glucosidase, β-galactosidase and β-*N*-acetylglucosaminidase from jack bean. For **1** to be suitable as an alternative to acarbose for diabetes, further modifications would be needed to make it more specific. However, hexosaminidase activity is elevated in many diseases including Alzheimer's[10] and so perhaps this inhibition is of more interest if selectivity can be improved. There are also indications that azasugars can improve the folding and function of glucohydrolases which can become aberrant in disease states including Alzheimer's.[10,12]

4. Conclusions

We have succeeded in the second racemic synthesis of tiruchanduramine and are currently investigating an asymmetric Henry reaction to effect a stereoselective synthesis of tiruchanduramine.[13] Synthetic **1**, displayed a broader range of inhibition than reported previously and, in addition to α-glucosidases, **1** also inhibits almond β-glucosidase, β-galactosidase and β-*N*-acetylglucosaminidase from jack bean.

5. Experimental

Column chromatography was carried out on silica gel (60 Å, 40−63 μm) and TLCs were conducted on precoated Kieselgel 60 F254 (Art. 5554; Merck) with the eluent specified in each case. All non-aqueous reactions were conducted in oven-dried apparatus under a static atmosphere of argon. Diethyl ether, THF and dichloromethane were dried by a Pure Solv MD-3 solvent