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Isolation and synthesis of a novel β-carboline guanidine derivative tiruchanduramine from the Indian ascidian *Synoicum macroglossum*☆

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Abstract—The isolation and synthesis of the racemic form of a novel β-carboline guanidine alkaloid, tiruchanduramine, a potent α-glucosidase inhibitor from the Indian ascidian, *Synoicum macroglossum* has been achieved.

1. Introduction

In recent years marine ascidians have been the focus of intensive chemical investigation as they are very rich sources of biologically active secondary metabolites.[1] A major group of these metabolites are nitrogen containing compounds, particularly aromatic heterocycles. As part of our ongoing investigation on bioactive compounds from marine organisms[2] we describe the isolation of a novel β-carboline guanidine alkaloid tiruchanduramine **1** isolated from an ascidian *Synoicum macroglossum*, which was collected at Tiruchandur, Tamilnadu, India during February 2002. A literature survey revealed that the genus *Synoicum* has yielded several tetraphenolic bis-spiroketals and different rubrolides.[3] In the present study the dichloromethane/methanol (1:1) extract of the ascidian was partitioned between water and EtOAc. The water extract was freeze-dried, and the residue was triturated with MeOH. The soluble material was subjected to gel filtration [Sephadex LH-20, dichloromethane/methanol (1:1)], followed by silica gel column chromatography eluting with $CHCl_3$/MeOH 80:20 to yield tiruchanduramine **1**.

Compound **1** was obtained as semi-solid, $[\alpha]_D$ +31 (*c* 0.5, MeOH) and showed a molecular mass ion at *m/z* 323 $[M+1]^+$, which afforded the formula $C_{17}H_{19}N_6O$ by HRFABMS (calcd 323.162, found 323.1613). The IR bands at ν_{max} 3221 (NH), 1681 (guanidine) and 1622 (amide) pointed to a guanidine derivative, and UV absorptions at λ_{max} (MeOH) 215, 234, 270, 334 and 347 nm indicated the presence of a β-carboline chromophore.[4] The structure of compound **1** was established by study of the ^1H, ^{13}C and 2D NMR data.

The ^1H NMR spectrum of compound **1** (Table 1) showed signals at δ 8.20 (1H, d, J = 8.0 Hz), 7.28 (1H, t, J = 7.6 Hz), 7.58 (1H, t, J = 7.6 Hz) and 7.63 (1H, d, J = 8.0 Hz) for an *ortho*-disubstituted benzene ring. Two aromatic 1H singlets at δ 8.85, 8.81 and a D_2O exchangeable signal at δ 12.10 (1H, s) pointed together with the UV data to a 3- or 4-substituted β-carboline moiety,[5] which was supported by the ^{13}C NMR spectrum (Table 1). The ^1H NMR spectrum displayed further signals in the aliphatic region at δ 3.99 (1H, m), 3.77 (1H, t, J = 9.6 Hz), 3.25 (1H, dd, J = 8.2, 9.6 Hz), 3.42 (2H, m) and 1.82 (2H, m). The linear connectivity of these aliphatic signals was established by a H,H COSY spectrum. The ^{13}C NMR spectrum (Table 1) of compound **1** displayed 17 carbon signals, which

Keywords: Ascidian; *Synoicum macroglossum*; Tiruchanduramine; β-carboline; α-Glucosidase inhibitor.

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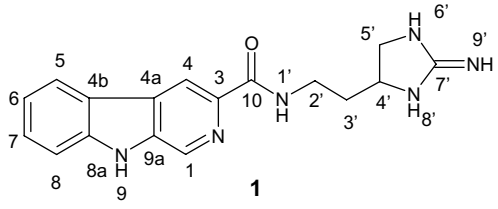
Table 1. NMR data of tiruchanduramine **1**

Carbon #	^{13}C NMR[a]	^{1}H NMR (J in Hz)[b]	H,H COSY	HMBC
1	132.2	8.85 (1H, s)	—	3, 4, 9a
2	—	—	—	—
3	139.5	—	—	—
4	113.9	8.81 (1H, s)	—	3, 10, 4b, 4a, 9a
4a	128.16	—	—	—
4b	120.9	—	—	—
5	122.1	8.20 (1H, d, J = 8.0)	6	4a, 8a, 7
6	119.9	7.28 (1H, t, J = 7.6)	5, 7	7, 8a, 8
7	128.5	7.58 (1H, t, J = 7.6)	6, 8	5, 8a
8	112.2	7.63 (1H, d, J = 8.0)	7	4b, 6
8a	141.0	—	—	—
9	—	12.10 (1H, br s)	—	—
9a	137.1	—	—	—
10	165.1	—	—	—
1′	—	8.84 (1H, s)	—	10
2′	35.2	3.42 (2H, m)	3′	10, 3′, 4′
3′	34.9	1.82 (2H, m)	2′, 4′	2′, 4′, 5′
4′	52.9	3.99 (1H, m)	3′, 5′	3′, 2′, 5′, 7′
5′	47.9	3.77 (1H, t, J = 9.6 Hz), 3.25 (1H, dd, J = 8.2, 9.6 Hz)	4′	4′, 3′, 7′
6′,8′,9′	—	7.80 (2H, br s) 8.18 (1H, br s)	—	—
7′	159.2	—	—	—

[a] 75 MHz.
[b] 300 MHz, DMSO-d_6.

included 11 aromatic and 4 aliphatic carbons, an amide carbonyl at δ 165.1 and a guanidine carbon at δ 159.2.

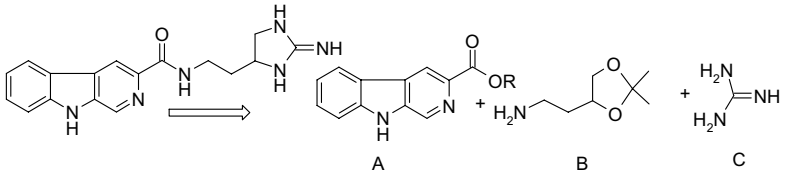


1

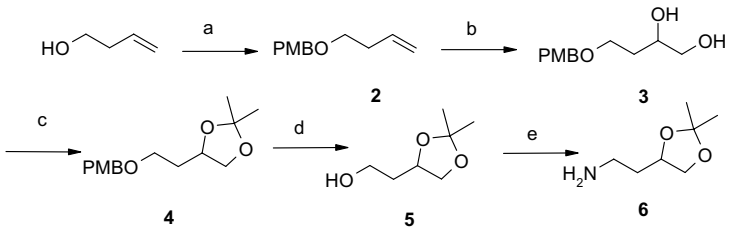
The structure of compound **1** was finally established by HMBC correlations. In the HMBC spectrum, the proton signals at δ 3.99 (4′-H, m), 3.77 (5′-H_A, t, J = 9.6 Hz) and 3.25 (5′-H_B, dd, J = 8.2, 9.6 Hz) showed cross-signals with the guanidine carbon C-7′ at δ 159.2. The ^{1}H and ^{13}C NMR signals of the side chain are comparable with the related guanidino amino acid in enduracidins.[6] Further, in the HMBC spectrum, the signals at δ 3.42 (2′-H_2, m) and 8.81 (4-H, s) showed correlations with the carbonyl signal of C-10 at δ 165.1. From the foregoing spectral data, the structure of tiruchanduramine was confirmed as **1**. Several ascidians, for example, *Eudistoma olivaceum* are extraordinarily rich sources of bromo-, hydroxy-, pyrrolyl- and 1-pyrrolinyl-β-carbolines.[7] Similarly, the ascidians *Eudistoma glaucus*[8] and *Lissoclinum fragile*[9] also contain β-carboline derived alkaloids. To the best of our knowledge β-carboline-3-carboxylates have not been reported from ascidians, however, the presence of β-carboline-3-carboxylates in human urine, brain tissue and bacteria is known.[5] Tiruchanduramine **1** is the first natural product containing enduracididinamine, the decarboxylation product of enduracididine, a rare amino acid obtained by hydrolysis of enduracidin[6] from *Streptomyces fungicidicus*. The absolute stereochemistry has not yet been established.

2. Synthesis of (±)-tiruchanduramine

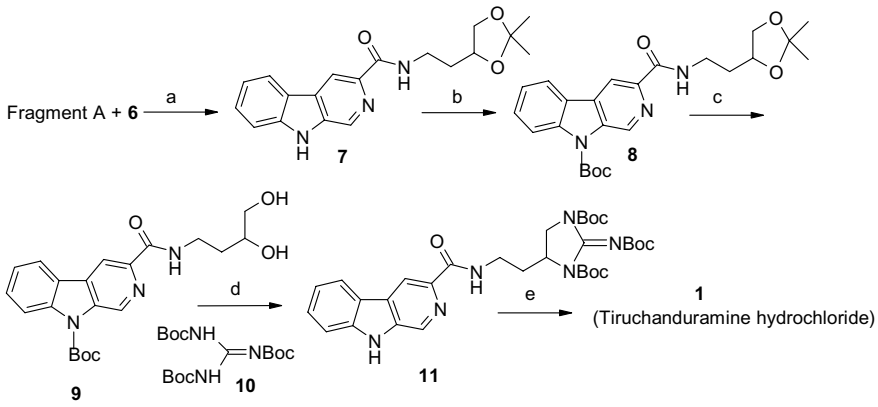
In order to confirm the structure of tiruchanduramine, we have synthesized compound **1** in racemic form. The retrosynthetic analysis (Scheme 1) revealed three main fragments, β-carboline-3-carboxylic acid (A), aliphatic side chain (B) and guanidine (C). Fragment A was synthesized following a literature procedure[10,11] in good yields, starting from L-tryptophan. Fragment B was prepared from homoallyl alcohol (Scheme 2).



Scheme 1.



Scheme 2. Reagents and conditions: (a) PMBBr, NaH, THF, 92%; (b) OsO_4, NMO, acetone/water 7:3, 70%; (c) 2,2-DMP, PTSA, 82%; (d) DDQ, DCM/water 9:1, 90%; (e) (i) *p*-TsCl, Py, 0 °C, 80%, (ii) NaN_3, DMF, 86%, (iii) 10% Pd/C, H_2, 92%.



Scheme 3. Reagents and conditions: (a) DCC, DMAP, DCM, 62% or EDCI, HOBT, dry DMF, 65%; (b) $(Boc)_2O$, Et_3N, DCM, 92%; (c) PPTSA, MeOH, 90%; (d) **9**, TPP, DEAD, THF, 52%; (e) 2 M HCl, MeOH, rt, 4 h 63%.

But-3-en-1-ol was protected with *p*-methoxybenzyl bromide to give compound **2**, which on dihydroxylation under standard conditions gave the diol **3**. The diol was then protected as the acetonide to give compound **4**. The *p*-methoxybenzyl group in **4** was removed using DDQ to give the primary alcohol **5**, which was converted into the amino-acetonide[12] **6** with in an overall yield of 37% (Scheme 2).

The amino-acetonide **6** and fragment A were coupled to give compound **7**, which was protected using Boc anhydride to yield compound **8**. The acetonide group in **8** was removed under acidic (PPTSA) conditions to afford the diol **9**.[13] The diol **9** was reacted with *N*,*N*′*N*″-tri-Boc-guanidine **10**[14] under Mitsunobu conditions to give Boc-protected tiruchanduramine **11** in 52% yield. Finally, the Boc groups were deprotected under acidic conditions[15] to give tiruchanduramine hydrochloride (**1**) (Scheme 3), the NMR data of which were identical with those of the natural product.

Tiruchanduramine **1** showed promising α-glucosidase inhibitory activity (IC_{50} 78.2 μg/mL) as compared with acarbose[16] at 100 μg/mL as the standard.

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13. All the compounds gave satisfactory analytical and spectral data. Compound **7**: Solid, mp 203–205 °C; IR (KBr): ν_{max} 3415, 1637, 1527, 1350, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (3H, s), 1.46 (3H, s), 1.96 (2H, m), 3.65 (3H, m), 4.12 (1H, dd, J = 7.0, 6.0 Hz,), 4.28 (1H, m), 7.32–7.46 (1H, m), 7.60 (1H, m), 7.82 (1H, br t), 8.20 (1H, d, J = 8.0 Hz), 8.50 (1H, br t), 8.82 (1H, s), 8.9 (1H, s), 9.54 (1H, br s); FABMS: 340 (M^++1); HRMS, obsd *m/z* 340.4019 $C_{19}H_{22}N_3O_3$ requires *m/z* 340.4021 [M^++1]; Compound **9**: Solid, mp 118.5 °C; IR (KBr): ν_{max} 3424, 2939, 2361, 1734, 1671, 1528, 1455, 1356, 1281, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.72 (2H, m), 1.80 (9H, s), 2.36 (1H, br s), 3.08 (1H, br s), 3.44 (1H, m), 3.56 (1H, dd, J = 8.0, 6.4 Hz), 4.64 (1H, dd, J = 8.0, 2.0 Hz), 4.80 (1H, m), 4.00 (1H, m), 7.42 (1H, t, J = 7.0 Hz), 7.64 (1H, t, J = 7.0 Hz), 8.10 (1H, d, J = 7.6 Hz), 8.46 (1H, t, J = 7.0 Hz), 8.78 (1H, s), 9.42 (1H, s); ^{13}C NMR: (75 MHz, MeOH-d_4): 27.9, 29.5, 34.1, 37.7, 67.3, 71.4, 86.7, 113.8, 117.3, 122.2, 124.5, 124.9, 131.1, 133.6, 137.1, 137.4, 140.4, 144.5, 151.2, 166.8; FABMS: 400 (M^++1); HRMS, obsd *m/z* 400.1872 $C_{21}H_{26}N_3O_5$ requires *m/z* 400.1879 [M^++1].
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