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6′,7′-Dihydrokeramamine C and analogues: synthesis and biological evaluation

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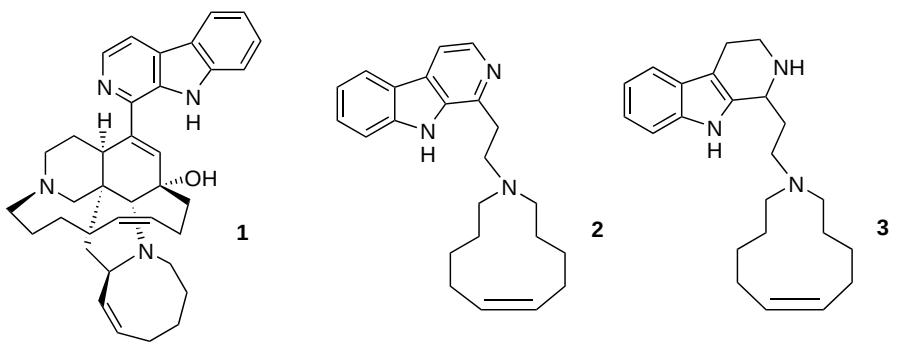
Abstract—6′,7′-Dihydrokeramamine C **7d** and analogues have been synthesised and evaluated for their cytotoxicity. Compound **7f** in which the azacycloundecane ring has been substituted by a dihexylamino unit showed increasing biological activity.

1. Introduction

Manzamine alkaloids[1] are a new family of cytotoxic natural products isolated from several Okinawan marine sponges. Manzamine A **1**[2] has the highest biological activity but manzamine C **2**,[3] which possesses the simplest structure among these alkaloids, still retains a significant cytotoxicity. Keramamine C **3**, a possible biogenetic precursor of manzamine C **2**, has been later isolated[4] (Scheme 1). Structure–activity relationship of manzamine C **2** has been also examined.[5] The role of the β-carboline unit and its possible interaction with DNA through GC intercalation has been emphasised. As far as we know, the biological activity of tetrahydro-β-carboline analogues of manzamine C **2**, like keramamine C **3**, has never been reported. As part of a program oriented towards the total syntheses of manzamine alkaloids,[6] in this report we describe a new straightforward synthetic route to dihydrokeramamine C **3** and congeners and the biological evaluation of these compounds.

2. Synthesis of dihydrokeramamine C 7d and analogues

A straightforward two step strategy has been developed for the synthesis of these tetrahydrocarboline derivatives. Accordingly, acrylonitrile was added dropwise to secondary amines **4a**–**4d** (1 equiv.). After 48 h at room temperature, the reaction mixture was distilled in vacuo, affording aminonitriles **5a**–**5d** in moderate to good yields. Aminonitriles **5a**–**5d** and **5e**, **5f**, which are commercially available, were then condensed with tryptamine derivatives **6a**–**6d**[7] in acetic acid under an



Scheme 1.

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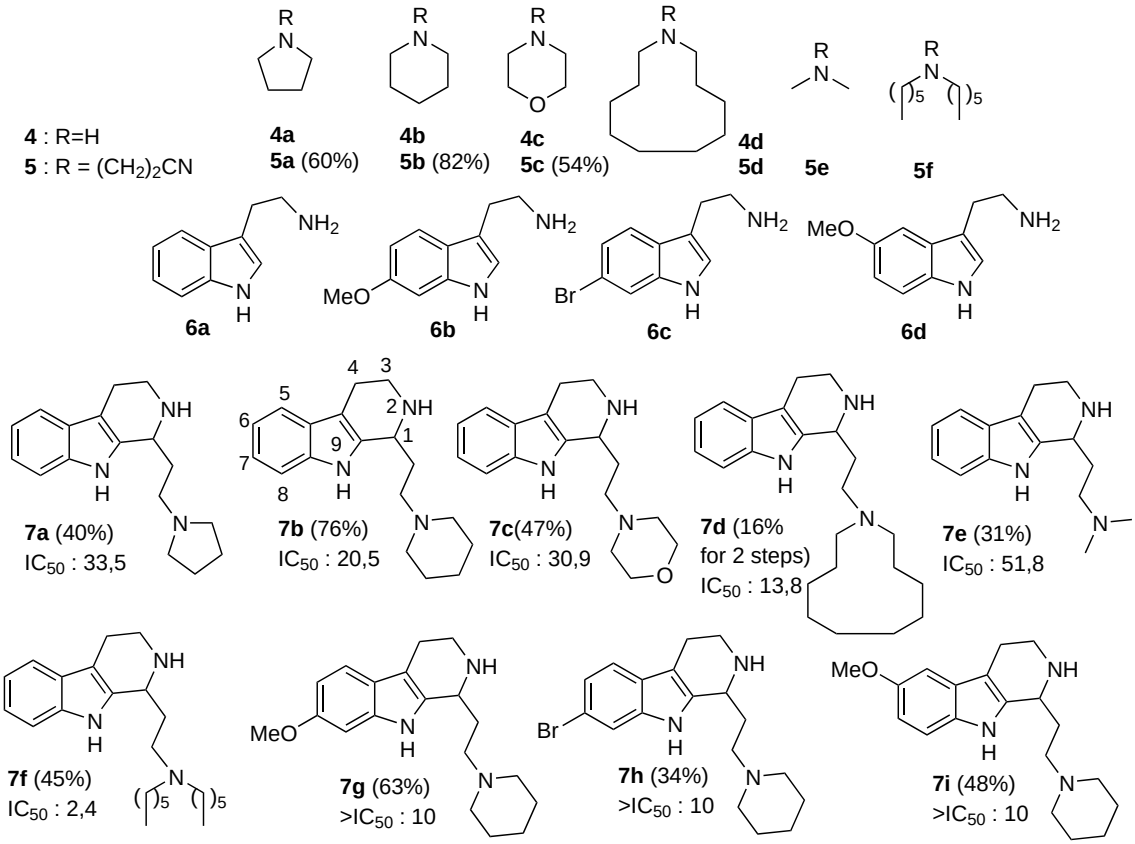

Scheme 2. (IC_{50} μM).

hydrogen atmosphere in the presence of palladium on charcoal,[8] according to the method of Lévy and colleagues.[9] After 20 h at room temperature, tetrahydrocarbolines **7a**–**7i**[10] were isolated after chromatographic purification in modest to good yields (Scheme 2).

3. Biological evaluation

Compounds **7a**–**7i** were evaluated for their antiproliterative activity using the murine L1210 leukaemia cell line.[11] The results expressed as IC_{50} values (concentration reducing by 50% cell proliferation) are reported in Scheme 2. It appears that the presence of a fully aromatised β-carboline unit is not essential to the activity.[12] The azacycloundecane ring in **7d** can be advantageously replaced by aliphatic hydrophobic side chains as in compound **7f**. Otherwise, substitution on the indole ring in compounds **7g**–**7i** seems to have little influence on cytotoxicity.

4. Conclusion

This study describes a direct access to keramamine C **3** congeners and demonstrates that some of these structurally simple compounds display significant cytotoxicity.

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7. 5-Methoxy tryptamine **6d** has been prepared according to: Taniguchi, M.; Anjiki, T.; Nakagawa, M. *Chem. Pharm. Bull.* **1984**, *32*, 2544.
8. With 6-bromo tryptamine **6c**, Rh-Al_2O_3 was used instead of Pd-C which induced an undesired hydrogenolysis of bromine.

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10. Selected data: ^{1}H NMR (200 MHz, δ ppm, TMS = 0, $CDCl_3$): compound **7b** ^{1}H NMR: 12, 1H, N_9-H; 7.48, 1H, d, 7.34, 1H, d, 6.98–7.18, 2H, m, C_5-H, C_8-H, C_6-H and C_7-H; 4.13–3.98, 1H, m, C_1-H; 3.58–3.30, 1H, m, C_3-H; 3.11–2.92, 1H, m, C_3-H; 2.88–2.21, 9H, m, C_4-H_2, NCH_2×3, N_2-H; 2.08–1.91, 1H, m, and 1.88–1.46, 7H, m, CH_2×4. ^{13}C NMR (50 MHz, $CDCl_3$): 136.6, C_{8a}; 135.6, C_{4b}; 127.6, C_{9a}; 120.8, C_6; 118.6, C_5; 118.0, C_7; 111.0, C_8; 107.2, C_{4a}; 58, C_3; 55.9, C_1; 54.2, NCH_2×2; 44.0, NCH_2; 32.5, CH_2; 25.9, C_4; 24.1, CH_2; 22.6, CH_2×2. Compound **7e** ^{1}H NMR: 10.90, 1H, N_9-H; 7.51, 1H, dd, 7.29, 1H, dd, 7.12, 2H, dt, C_5-H, C_8-H, C_6-H and C_7-H; 4.10, 1H, t, C_1-H; 3.37 and 3.01, 2H, m, C_3-H_2; 2.92–2.68, 3H, m, N_2-H and C_4-H_2; 2.61, 1H, m, and 2.42, 1H, m, CH_2; 2.26, 6H, s, $N(CH_3)_2$; 1.91, 2H, m, CH_2. ^{13}C NMR (50 MHz, $CDCl_3$): 135.9 and 135.7, C_{4b} and C_{8a}; 127.5, C_{9a}; 121.0, 118.7, 118.0 and 111.1, C_5, C_6, C_7 and C_8; 107.6, C_{4a}; 58.0, C_4; 54.6, C_1, 45.2, $N(CH_3)_2$; 43.3, C_3; 32.8, CH_2; 22.4, CH_2. Compound **7g** ^{1}H NMR: 8.71, 1H, s, N_9-H; 7.34, 1H, d, 6.83, 1H, s and 6.71, 1H, s, C_6-H, C_8-H, C_5-H; 4.12–3.95, 1H, m, C_1-H; 3.79, 3H, s, OCH_3; 3.42–2.72, 2H, m, C_3-H_2; 2.72–2.10, 9H, m, N_2-H, C_4-H_2, CH_2×3; 2.14–1.86, 1H, m, and 1.74–1.22, 7H, CH_2×4. ^{13}C NMR (62.5 MHz, $CDCl_3$): 155.7, C_7; 136.4, C_{8a}; 135.0, C_{9a}; 122.2, C_{4b}; 118.4, C_5; 107.7, C_6; 106.9, C_{4a}; 95.5, C_8; 57.8, C_3; 55.9, C_1; 54.6, NCH_2×2; 43.6, NCH_2; 32.0, CH_2; 26.1, C_4; 24.2, CH_2; 22. 4, CH_2×2. Compound **7h** ^{1}H NMR: 8.48, 1H, N_9H; 7.43, 1H, s, 7.29, 1H, d, 7.11, 1H, d, C_8-H, C_6-H and C_5-H; 4.16–3.88, 1H, m, C_1-H; 3.53–3.28, 1H, m and 3.12–2.82, 1H, m, C_3H_2; 2.73–2.12, 9H, m, N_2-H, C_4-H_2, NCH_2×3; 2.05–1.84, 1H, m, and 1.80–1.38, 7H, m, CH_2×4. ^{13}C NMR (62.5 MHz, $CDCl_3$): 137.4, C_{8a}; 136.4, C_{4b}; 126.6, C_{9a}; 121.7, C_5; 119.2, C_6; 114.0, C_7; 113.7, C_8; 58.0, C_3; 56.0, C_1; 54.7, NCH_2×2; 43.9, NCH_2; 32.7, CH_2; 26.1, C4; 24.2, CH_2; 22.4, CH_2× 2.
11. L1210 murine leukaemia cells were grown in RPMI 1640 medium supplemented with 10% foetal calf serum, 2 mM L-glutamine, 100 units/mL penicillin, 100 μg/mL streptomycin and 10 mM HEPES buffer. Cells were exposed to graduated concentrations of the compounds. After incubation for 48 h at 37°C, cell proliferation was measured by MTT essay (Alley, M. C; Scudiero, A.; Monks, M. L.; Cserwinski, M. J.; Fine, D. L.; Abott, B. J.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Cancer Res*., **1988**, *48*, 589.). Results are expressed as IC_{50}.
12. Other manzamine type alkaloids devoided of β-carboline unit also showed significant cytotoxicity, see Ref. 1c.