UNIVERSITI TEKNOLOGI MARA

SYNTHETIC APPROACH TOWARDS ANTI-INFLAMMATORY AGENT, DAIBUCARBOLINE A AND ITS DERIVATIVES *VIA* TETRAHYDRO-β-CARBOLINE INTERMEDIATES

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ABSTRACT

β-Carbolines, belonging to the class of indole alkaloids, were isolated from wild Syrian rue (*Peganum harmala*), which is common in Iran. Over the past few decades, the synthesis of β-carbolines has elicited much interest due to its wide pharmaceutical and biological applications. For instance, one of their many derivatives, the daibucarboline A **1**, is proved to demonstrate interesting anti-inflammatory activity upon tested using iNOS assay with the IC_{50} value of 18.41 μM. However, literature survey reveals there is no report found on the synthesis of daibucarboline A **1** in addition to limited works on its isolated compound. Thus, we described herein the synthetic approach towards daibucarboline A **1** and its derivatives by using different substituted indoles and aldehydes/glyoxal. The first part is the chemical studies towards the intermediates and derivatives of daibucarboline A **1** using tryptamine **29** as the starting material with different substituted benzaldehydes **30-42** to afford a series of key 1-substituted tetrahydro-β-carboline intermediates **43-55** in 20-95 % yields. Subsequent removal of hydrogens to promote aromatization of the intermediates *via* oxidative dehydrogenation reaction, mediated by I_2 and H_2O_2 furnished the aromatized β-carboline **56-60** in 42-83 % yield. Having β-carboline **56-60** in hand, the reaction proceeded with the insertion of methyl substituent on N-1 position of the indole moiety in the presence of NaH and alkylating agent, CH_3I *via N*-alkylation to afford *N*-methylated derivatives **61** and **62** in 43-58 %. The second part is the chemical studies towards the intermediates and derivatives of daibucarboline A **1** using 5-hydroxy-L-tryptophan **63** as the starting material with different substituted phenylglyoxals **64-69** to furnished derivative **72-76** via Pictet-Spengler cyclization. The reaction proceeded with the reduction of carbonyl functionality *via* Wolff-Kishner reduction using hydrazine hydrate and KOH to furnish derivatives **80-84** in moderate yields of 38-56 %. Fischer esterification and carbonyl reduction were also attempted on starting material **63** to give derivatives **77** and **78** respectively. In the final step, subsequent conversion of derivative **84** to an ether derivative **85** was achieved *via* Williamson ether synthesis in 61 % yield. The essential derivative **85** towards daibucarboline A was successfully synthesized in four steps with an overall yield of 3.4 %. The third part is the screening of anti-inflammatory activities of daibucarboline A and its derivatives using xanthine oxidase inhibitory assay. At the concentration of 100 μg/mL, 27 compounds showed anti-inflammatory activities against xanthine oxidase, ranging from weak to moderate inhibitory effect. Compounds **58**, **72**, **74**, **75, 81** and **83** were found to moderately inhibit the production of xanthine oxidase with compound **81** showed the highest inhibitory effect of 63.17 % inhibition. The structures of all synthesized intermediates and derivatives of β-carboline were confirmed by NMR, FTIR and GC-MS spectroscopy.

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