UNIVERSITI TEKNOLOGI MARA

SYNTHESIS TOWARDS NEMONAPRIDE AND ITS DERIVATIVES

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MSc

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AUTHOR DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Nemonapride **1**, was introduced into pharmaceutical industry by a Japanese company, Yamanouchi Co. Ltd. in 1991. It has a unique *N*-benzyl-pyrrolidine moiety bonded to an amide functional group, linking the substituted benzene ring. Nemonapride or commercially known as emilace, is an atypical antipsychotic drug used for the treatment of schizophrenia. Since the number of patients nowadays has been increasing, global demand for antidepressant and antipsychotic medicines such as nemonapride increases too. In this study, an efficient synthetic strategy towards synthesizing nemonapride and their derivatives was constructed by using 2,4-pyrrolidinedione (tetramic acid) as the key intermediate. In the first part, derivatives of tetramic acid **5**, **91** and **95** were synthesized from several amino acid methyl esters using a stepwise reaction which includes condensation, Dieckmann cyclization and decarboxylation. In the second part, only the synthesized tetramic acid **5** proceeded further that was reduced to form hydroxypyrrolidine **11** and hydroxylactam pyrrolidine **14**, while at the same time underwent amination reaction that produced oxime **98** and enamine **99**. Towards the synthesis of aminopyrrolidine **2**, the hydroxyl group on **11** underwent a substitution reaction to produce *O*-mesylated **96** and azide-pyrrolidine **97**. The final part focused on synthesizing nemonapride and its derivatives using the synthesized intermediate via peptide coupling and esterification reactions. Substituted benzoic acid **3** was synthesized from substituted benzoate as the starting material which was then condensed with the intermediates **11**, **14** and **99**. A few methods were employed which then only the acylated **101** was obtained. Nevertheless, none of the nemonapride-skeleton-alike was successfully synthesized.

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