UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, IN-VITRO BIOACTIVITY EVALUATION AND MOLECULAR DOCKING OF MONOSACCHARIDE ESTER AND FATTY ACID AMIDE DERIVATIVES OF 5-AMINOSALICYLIC ACID

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By

SAMIRA YOUSEFI

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DEDICATION

"To my beloved parents, brother and grand parents, for their unconditional love, patience and support, which made this journey possible for me."

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

SYNTHESIS, IN-VITRO BIOACTIVITY EVALUATION AND MOLECULAR DOCKING OF MONOSACCHARIDE ESTER AND FATTY ACID AMIDE DERIVATIVES OF 5-AMINOSALICYLIC ACID

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May 2016

Chairman : Emilia bt Abd Malek, PhD
Faculty : Science

5-aminosalicylic acid (5-ASA), structurally related to the salicylates, is active in the treatment of inflammatory bowel disease (IBD). Since IBD is a high-incidence disease and considering that 5-ASA has been approved as one of the most effective and tolerable drug for the majority of patients in treatment of IBD, up to date, varied derivatives with slightly different formulation of 5-ASA have been prepared to allow it to reach different areas of the bowel and to help keep the condition in remission. On the other hand, according to the documentary evidences on the remarkable properties of fatty acids and saccharides in various areas especially in pharmaceutical field, they have been proposed as beneficial candidates for conjugating with drugs in order to enhance drugs' bioavailability. Therefore, in this work, a series of new monosaccharide selective ester derivatives of 5-ASA including galactose, fructose, glucose and xylitol esters and new fatty acid amide derivatives of 5-ASA including lauric, linoleic and oleic amide, were synthesized to study their anti-bacterial, anti-inflammatory and cytotoxicity activities in comparison with initial drug. The structures of all the produced compounds (sixteen compounds: including eleven unknown compounds and five known intermediates) were confirmed by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR and DIMS). Following that, the above-mentioned *in vitro* bioactivity evaluation was performed for all new final ester and amide derivatives of 5-ASA (four monosaccharide ester and three fatty acid amide derivatives). The antibacterial activity evaluation of them against Gram-negative bacteria and Gram-positive bacteria revealed that all were more effective against Gram-negative as well as Gram-positive bacteria than the parent drug (5-ASA) which showed insignificant activity. Furthermore, they were confirmed by the cytotoxicity assay over HT-29 and 3T3 cell lines to be less toxic for normal cells (3T3 cells) compared to the parent drug. On the other hand, however, their suppressive effect against colon cancerous cells (HT-29 cells) was somewhat lower. Meanwhile, the anti-inflammatory assay over RAW264.7 macrophage cell line demonstrated NO (nitric oxide) inhibition activity of these new derivatives of 5-ASA, moderately has improved in comparison with the parent drug. Although the mechanism of action of 5-ASA is still is unknown, but the clinical effectiveness of 5-ASA attributed to its inhibition effect on cyclooxygenase (COX-1/COX-2) and lipoxygenase (5-LOX) enzymes' pathways which are playing a vital role

in the inflammation process to produce inflammatory mediators. To predict the possible interactions and binding energy of the new compounds against these proteins, *in-silico* screening via molecular docking technique was performed and the new products exhibited greater hydrogen bonding and greater binding affinities with the active sites of proteins towards 5-ASA. As conclusion, eleven new monosaccharie ester and fatty acid amide derivatives of 5-ASA were synthesized successfully in average yields and showed approximately moderate to superior bioactivities for above-mentioned assays than 5-ASA which may help for drug development in future. Also, molecular docking was performed against two enzymes involved in the inflammation process to predict the possible interactions and binding energy of the new compounds for future *in-vivo* experimental works.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

SINTESIS, PENILAIAN BIOAKTIVITI SECARA IN-VITRO DAN DOK MOLEKUL BAGI DERIVATIF ESTER MONOSAKARIDA DAN AMIDA ASID LEMAK DARIPADA ASID 5-AMINOSALISILIK

Oleh

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Asid 5-aminosalisilic (5-ASA), berkait rapat secara struktur dengan salisilat, yang aktif dalam penyakit keradangan usus (IBD). Disebabkan IBD adalah penyakit yang paling kerap berlaku dan memandangkan 5-ASA telah diluluskan sebagai ubat yang paling berkesan dan boleh diterima bagi majoriti pesakit dalam rawatan IBD, sehingga kini, pelbagai derivatif dengan sedikit perubahan terhadap 5-ASA telah disediakan untuk membolehkan ia untuk sampai ke kawasan yang berbeza-beza dalam usus dan membantu dalam penyembuhan. Selain daripada itu, sesuai dengan bukti-bukti dokumentari mengenai sifat-sifat mengagumkan daripada asid lemak dan sakarida dalam pelbagai bidang terutama dalam bidang farmaseutikal, mereka telah dicadangkan sebagai calon bermanfaat untuk dicantumkan dengan ubat-ubatan untuk meningkatkan kadar serapan dadah ke dalam tisu badan. Satu siri ester selektif terhadap monosakarida 5-ASA termasuk ester galaktosa, fruktosa, glukosa dan xilitol, dan asid lemak amida terbitan 5-ASA termasuk amida laurik, linoleik dan oleik yang baru telah disintesis bagi mengkaji aktiviti anti-mikrob, anti-kanser dan anti-radang mereka berbanding dengan ubat asal. Struktur bagi semua sebatian yang dihasilkan (enam belas sebatian termasuk sebelas sebatian tidak diketahui dan lima sebatian diketahui) telah disahkan menggunakan kaedah spektroskopi (^{1}H NMR, ^{13}C NMR, IR and DIMS). Berikutan itu, penilaian bioaktiviti *in vitro* seperti yang telah disebutkan telah dijalankan ke atas kesemua derivatif ester dan amida 5-ASA (empat derivative ester monosakarida dan tiga derivatif amida asid lemak.) Aktiviti antibakteria bagi produk baru ini telah diuji terhadap bakteria Gram-negatif dan bakteria Gram-positif. Keputusan penilaian aktiviti anti-bakteria mendapati kesemua sebatian baru lebih berkesan terhadap Gram-negatif dan juga bakteria Gram-positif berbanding sebatian asal (5-ASA) yang menunjukkan aktiviti yang tidak ketara. Tambahan pula, mereka telah disahkan melalui penilaian sitotoksik terhadap bahagian sel HT-29 dan 3T3 sebagai kurang toksik terhadap sel normal (sel 3T3) berbanding sebatian asal. Walaubagaimanapun, kesan sekatan terhadap sel kanser kolon (sel HT-29) adalah lebih rendah. Sementara itu, penilaian anti-radang bagi semua

produk baru terhadap sel makrofaj RAW264.7 telah menunjukkan peningkatan sederhana bagi perencatan aktiviti nitrik oksida (NO) berbanding sebatian induk. Walaupun mekanisme tindakan 5-ASA masih tidak diketahui, tetapi keberkesanan klinikal 5-ASA dikaitkan dengan kesan perencatan pada siklooksigenase (COX -1 / COX- 2) dan laluan lipooksigenase (5- LOX) enzim yang memainkan peranan penting dalam proses keradangan untuk menghasilkan pengantara keradangan. Untuk meramalkan interaksi mungkin dan tenaga pengikat sebatian baru terhadap protein ini saringan *in-silico* melalui teknik dok molekul telah dilakukan dan produk baru mempamerkan ikatan hidrogen dan affiniti pengikatan yang lebih besar terhadap tapak aktif protein berbanding 5-ASA. Kesimpulannya, sebelas derivatif ester monosakarida dan asid lemak amida 5-ASA yang baru telah berjaya disintesis dengan hasil purata dan menunjukkan bioaktiviti yang sederhana atau lebih baik bagi bioesei yang telah disebutkan berbanding 5-ASA yang boleh membantu pembangunan ubat-ubatan masa hadapan. Di samping itu, dok molekul telah dilakukan terhadap dua enzim yang terlibat dalam proses keradangan bagi meramalkan interaksi mungkin dan tenaga pengikatan sebatian baru untuk kerja-kerja eksperimental *in vivo* masa hadapan.

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I certify that a Thesis Examination Committee has met on 18 May 2016 to conduct the final examination of Samira Yousefi on her thesis entitled "Synthesis, In-Vitro Bioactivity Evaluation and Molecular Docking of Monosaccharide Ester and Fatty Acid Amide Derivatives of 5-Aminosalicylic Acid" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis submitted to the Senate of Universiti Putra Malaysia has been accepted as fulfillment of the requirments for the degree of Doctor of Philosophy. The members of the Supervisory committee were as follows:

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LIST OF ABBREVIATIONS

Δ	Chemical Shift
ΔG	Gibbes Energy
5-ASA	5-Amino salicylic acid
5-LOX	5-Lipoxygenase
ASA	Amino salicylic acid
c / conc.	Concentration / Concentrated
CADD	Computer-Assisted Drug Design
Calcd	Calculated
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIMS	Direct Infusion Mass Spectrometry
DMAP	Dimethylaminopyridine
DMSO	Dimethyl Sulfoxide
DHU or DCU	Dicyclohexyl urea
eq / equiv.	Equivalents
ESI	Electrospray Ionisation
Et_3N	Triethylamine
FDA	Food and Drug Administration
FT	Fourier Transformation
GC	Gas Chromatography
H	Hours
HOBT	Hydroxybenzotriazole
HOSU	*N*-hydroxysuccinimide
IBD	Inflammatory Bowel Disease
IR	Infrared (Spectroscopy)
J	NMR Coupling Constant
LT	Leukotriene
M	Molar
Min	Minutes
M.p	Melting Point
m/z	Mass to Charge Ratio
MS	Mass Spectroscopy
NMM	*N*-methylmorpholine
NA	Nutrient agar
NMR	Nuclear Magnetic Resonance
NSAID	Nonsteroidal Anti-inflammatory Drug
p	Para
PG	Prostaglandin
Ph	Phenyl
PLA_2	Phospholipase A2
QSAR	Quantitative Structure Activity Relationship
RMSD	Root-mean square deviation
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SD	Standard Deviation
S.E.M	Standard Error of the Mean
SP	Sulfapyridine

TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
TX	Thromboxane

CHAPTER 1

INTRODUCTION

Inflammatory bowel disease (IBD) is a high-incidence disease which is induced by a complex interplay among environmental, genetic and immunoregulatory factors (Hanauer, 2006, Giannini *et al.*, 2005). Also, IBD is a main risk factor for developing colorectal cancer which covers a wide range of patients' ages, (Friend, 2005, Giannini *et al.*, 2005, Tursi *et al.*, 2011). If IBD not treated properly, it can lead to outbreak of two major colon associated diseases, namely ulcerative colitis and Crohn's disease, (Yang *et al.*, 2014, Williams *et al.*, 2011, Giannini *et al.*, 2005, Friend, 2005). Therefore, high priority should be accorded to the achievement of better therapeutic effects for the treatment of IBD.

5-Aminosalicylic acid (5-ASA), (Figure 1.1) has been the most widely prescribed anti-inflammatory drug for recovering and maintaining the relapse of IBD due to its limited side effects and its tolerability for the majority of patients (Giannini *et al.*, 2005, Stolfi *et al.*, 2008, Tursi *et al.*, 2011). 5-ASA was approved by FDA (food and drug administration) in 1987 (Williams *et al.*, 2011, Couto *et al.*, 2010, Ahmad *et al.*, 2006) and in the market is known with different commercial brands such as mesalamine, mesalazine and asacol,. Both experimental and epidemiological studies have revealed that in long-term usage, 5-ASA represses gastrointestinal toxicity (Friend, 2005) and acts as a chemopreventive agent (Lopez *et al.*, 2012, Ahmad *et al.*, 2006, Ritland *et al.*, 1999) particularly against colitis-associated cancers (Campregher *et al.*, 2010).

5-ASA has been introduced as an antioxidant agent as well, since its scavenging effects has been verified against reactive oxygen and nitrogen species (ROS and RNS, respectively), (Couto *et al.*, 2010).

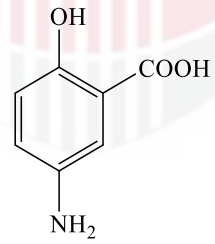

Figure 1.1 Structure of 5-ASA.

Unfortunately, to date, the exact mechanism of action and metabolism of 5-ASA has not entirely found yet, but it presumes that 5-ASA reduces inflammation by inhibiting cyclooxygenase and lipoxygenase enzymes' pathways which catalyze the production of prostaglandins and other inflammatory mediators in the intestine (Carmine *et al.*, 2008, Shiff 2003).

On the other hand, sugar drug derivatives have opened a new gateway in medicine and pharmaceutical fields and recently, a great number of drugs in use have relied on carbohydrates (Quan *et al.*, 2007b). It has been found that incorporation of carbohydrates with drugs improves permeation of the drugs into the cell membranes and increases delivery of drugs to the targeted site (Quan *et al.*, 2007b). Also it has been reported that glycosidic linkage, raises the water-solubility and stability of biocompatibility of drugs (Kohane *et al.*, 2002). Glycotargeting also has demonstrated that carbohydrate ligands can feasibly interact to target protein receptors at the sites of localization (Kuehl *et al.*, 2005). Not only the antimicrobial (Douglas L. Marshall *et al.*, 1994) and anti-tumor (Okabe *et al.*, 1999) properties of carbohydrates but also their anti-inflammatory characteristics in some synthetic compounds possessing glycosidic linkages (Soni *et al.*, 2014) have been proven thus, offering them a potential choice for conjugation to drugs in order to improve their biological activities.

Fatty acids (either saturated or unsaturated carboxylic acids with variable aliphatic chain lengths), are known for their health benefits (Williams, 2000, Field *et al.*, 2009) in cosmetic, pharmaceutical, and food industries (Adnani *et al.*, 2011a, Zhu *et al.*, 1989). They are mostly available in natural resources such as animal, vegetable fats and oils (Yang *et al.*, 2012, Adamopoulos, 2006). In medicine, fatty acid derivatives have wide applications due to their anti-obesitic, anti-carcinogenic, anti-atherogenic, anti-diabetogenic, immunomodulatory, apoptotic and osteosynthetic effects (Benjamin *et al.*, 2009). Fatty acids have exhibited activity in improving antibacterial properties of their derivatives (Adnani *et al.*, 2011a, Waterman *et al.*, 2007). Intracellular absorption of some derivatives of fatty acid are raised in the related tract because of fatty acids' amphipathic property (Fitscher *et al.*, 1996). Also, the mediation of fatty acid's moiety in enhancing anti-inflammatory and anti-tumour activities of some drug derivatives has introduced them as multivalent compounds.

1.1 Problem Statements

Despite the remarkable advantages of 5-ASA and producing its derivatives in order to improve therapeutic properties of this drug, patient life quality has so far not been improved. This is due to the fact that, when the drug is taken orally or used in the form of a suppository, the main portion of the drug is absorbed in the small intestine and hardly reaches the colon (Giannini *et al.*, 2005). Its low stability in the gastrointestinal tract (Abdu-Allah *et al.*, 2005) and poor water solubility (Aguzzi *et al.*, 2011, Aguzzi *et al.*, 2010, Zou *et al.*, 2005) are other problems which result in the necessary consumption of a higher dosage of the drug in order to be effective, the requirement of long-term treatment and a greater number of side effects. Also, in some cases, the disease relapses and surgery is required (Friend, 1991, Freeman, 2012, Williams *et al.*, 2011).

As regards, conjugation of drugs with saccharides and fatty acids offers a lot of opportunities to enrich bioavailability and pharmaceuticals properties, (Uhrig *et al.*, 2000, Jacob *et al.*, 2012, Chen *et al.*, 2004) in this current work, both monosaccharide ester derivatives and fatty acid amide derivatives of 5-ASA were synthesized to study some biological activities of this drug including antibacterial, anti-inflammatory and cytotoxicity activities in comparison with the parent drug.

In addition, preparation of 5-ASA's ester and amide derivatives was suggested because it has been found that ester bond is fairly fixed in the acidic medium and readily ruptured in the basic environment which is compatible with gut nature (Rajesh, 2011) and may enable the drug glycoside to release the active drug in the colonic tract through enzymatic action. It has also been reported that the amide bond is stable in the upper part of the intestine, and as a result a large quantity of the orally administered prodrug might be delivered to the colon where it will be degraded by amidases of microflora to release the drug (Abdu-Allah *et al.*, 2005).

Time and resources consuming processes are major problems in drug discovery and development. Computer-based analysis is utilized as a key tool in the field of molecular modelling to expedite and facilitate drug discovery and development processes. One of the useful computational techniques for exploring the interactions and binding energy of ligands into receptors is structure (target)-based design or molecular docking, (Charlier *et al.*, 2003, Palkar *et al.*, 2014, Hegazy *et al.*, 2012, Kapetanovic, 2008). Since cyclooxygenase and lipoxygenase proteins have been introduced to be effective in inflammation process, the behaviour of new compounds on COX-1, COX-2 and 5-LOX proteins was screened via *in silico* molecular docking and was compared with the original drug.

1.2 Goals and objectives of the study

Considering that to date there are no published reports on synthesis of monosaccharide and fatty acid derivatives of 5-ASA, hence, the objectives were set as follows:

1) To synthesize and characterize monosaccharide ester and fatty acid amide derivatives of 5-ASA.

2) To evaluate the *in-vitro* bioactivities of the new compounds including antibacterial, anti-inflammatory and cytotoxicity activities in comparison with 5-ASA.

3) To predict specifications of the new compounds onto effective enzymes in producing inflammatory mediators including COX-1, COX-2 and 5-LOX proteins via *in-silico* molecular docking in order to obtain further leads for drug design and discovery developments in future studies or experimental works.

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