UNIVERSITI TEKNOLOGI MARA

SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES OF MORPHOLINE AND COUMARIN DERIVATIVES

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ABSTRACT

Plant-based natural products have played a major role in the development of new drug candidates. Organic synthesis has overcome the limitation of the compounds from natural sources, which provide and develop new pharmaceutical products. In order to explore new therapeutic synthetic compounds, the morpholine scaffold had found to be an outstanding pharmacophore in medicinal chemistry and number of molecules having morpholine skeleton are the clinically a drug. Seventeen novel derivatives of morpholine were synthesised by different arylhydrazides and 5-morpholinothiophene-2-carbaldehyde. All synthesised compounds (**83-99**) were evaluated for their *in-vitro* anticancer potential against two human cancer cell lines, HepG2 and MCF7. Seventeen coumarin-based derivatives (**101-117**) were screened for α-glucosidase inhibitor activity and 3-formylcoumarin (**118-134**) analogues were screened for thymidine phosphorylase inhibition. All compounds showed a variable degree of inhibitions when compared to the standard inhibitors. Molecular docking studies were carried out to understand the binding interaction of active compounds. Analogues **95** had similar substantial inhibition effects towards HepG2 with IC_{50} value 6.76±3.12 μM, when compared with the standard doxorubicin (IC_{50} value 6.59±0.45 μM); while compounds **87**, **90** and **91** showed potent cytotoxicity against MCF7 with IC_{50} value 7.08±0.42 μM, 1.26±0.34 μM and 11.22±0.22 μM respectively, when compared with the standard tamoxifen (IC_{50}=9.53±0.40 μM). Coumarin-based derivatives, analogue **105** inhibition seems effective towards HepG2 and MCF7 with IC_{50} values 0.02±1.78 μM and 10.23±1.77 μM, respectively. Coumarin-based derivatives have been evaluated for α-glucosidase inhibitory potential, all derivatives exhibited outstanding α-glucosidase inhibition with IC_{50} values ranging between 1.10 ± 0.01 and 36.46 ± 0.70 μM when compared with the standard inhibitor acarbose having IC_{50} value 39.45 ± 0.10 μM. The most potent derivative among the series was analogue **103** (IC_{50}=1.10 ± 0.01 μM). 3-Formylcoumarin analogues were selected for thymidine phosphorylase inhibitory activity, since the series were not a favourable against HepG2 and MCF7 cell lines. Presents of chloro substituent of coumarin showed a variable degree of thymidine phosphorylase (TP) inhibition with IC_{50} values ranging between 0.90 ± 0.01 and 53.50 ± 1.20 μM when compared with the standard inhibitor 7-deazaxanthine having IC_{50} value 38.68 ± 1.12 μM. Fifteen analogues showed excellent inhibition better than the standard drugs with four analogues, **121**, **122**, **125** and **133** shown with IC_{50} 3.50 ± 0.10, 1.50 ± 0.01, 1.30 ± 0.10 and 0.90 ± 0.01, respectively. The structure-activity relationship (SAR) was mainly based upon by bringing about the difference of substituents on the phenyl ring. Molecular docking studies were carried out to understand the binding interaction of the active analogues with active site of enzyme.

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TABLE OF CONTENT

CHAPTER ONE
INTRODUCTION

1.1 Research Background

Heterocycles are frequently used as pharmaceutical products in drugs discovery program (Gomtsyan, 2012). Coumarin is a plant-derived natural product and identified for its wide range of pharmacological properties such as anti-inflammatory, anticoagulant, antibacterial, antifungal, antiviral, anticancer, antihypertensive, antitubercular, anticonvulsant, antiadipogenic, antihyperglycemic, antioxidant, and neuroprotective properties (Lacy & O'Kennedy, 2004). The synthesis of coumarin and its derivatives are quite famous and widely discovered by organic medicinal chemists for many years.

Morpholine was often used for corrosion fortification for the steam system of the power plant. Some of the morpholine derivatives are used as antioxidants, fungicides, insecticides, corrosion inhibitors, viscosity improvers, herbicides, local anaesthetics and antiseptics. Morpholine was first detected by Hamano *et al.* (1981).

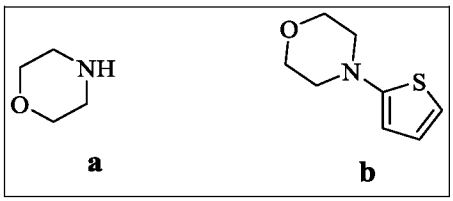

Figure 1.1 Morpholine (**a**) and Morpholinothiophene (**b**)

This colourless oily and volatile chemical are having a great importance for the different industrial purpose. Morpholine is a cheap solvent for waxes, resins, casein and dyes. Morpholine derivative, amorolfine use as an antifungal drug and the substituted morpholines verified with aesthetic properties. 4-Phenyl-morpholine derivatives were described to possess antimicrobial, anti-inflammatory and central nervous system activities (Hamano *et al.*, 1981; Xavier & Raj, 2013). Schiff bases have been reported to possess antimicrobial properties apart from other biological activities. The basic skeleton structure of morpholine (**a**) with its starting material (**b**) are shown in figure 1.1.