Abstract

This study includes the synthesis of new benzothiazole derivatives that were expected to have biological activity as anticancer agents

This study contains four chapters; the first one is an introduction which consists of a brief survey about the different methods used for the synthesis of 2-substituted benzothiazoles and an account on their anticancer activity.

The second chapter deals with the aim of the work and schemes that had been carried out to obtain the new required benzothiazole, thiazolidinone, urea, thiourea, amine, bis-benzothiazole and phenol derivatives.

The third chapter clarifies the theoretical discussion of the experimental work for the preparation of the starting materials **Ia-b**, **VI** and the target compounds **IVa-i - XVIa-c**.

In Scheme 1, the reaction of **Ia-b** with chloroacetyl chloride afforded the key intermediates **IIa-b** which upon cyclization with ammonium thiocyanate yielded thiazolidinones **IIIa-b.** As an extension, reaction of **IIIa-b** with different aryl and heteroaryl aldehydes afforded **IVa-i**. In addition, compound **IIb** was cyclized to give the unexpected compound **V** instead of nucleophillic substitution when reacted with different substituted anilines.

In Scheme 2, the reaction of **VI** with different aldehydes afforded the Schiff's compounds **VIIa-e** which upon cyclization with thioglycolic acid yielded thiazolidinones **VIIIa-e**.

Also in Scheme 3, the formation of urea and thiourea derivatives was constructed by reacting **VI** with 4-chlorophenylisocyanate and ethylisothiocyanate to obtain **IX** and **X** respectively. In addition, compound **X** was cyclized to give thiazolidinone **XI** using monochloroacetic acid through nucleophillic substitution reaction.

Also the reaction of **VI** with chloroacetyl chloride gave compound **XII** from which **XIIIa-c** were obtained *via* nucleophillic substitution with different primary and/or secondary amines. Furthermore, cyclization of compound **XII** with ammonium thiocyanate yielded thiazolidinone **XIV.**

Formation of bis-benzothiazole **XV** was achieved *via* reacting **IV** with potassium thiocyanate in presence of bromine as a catalyst.

Also the phenolic derivatives **XVIa-c** were formed *via* coupling of diazonium salt of **VI** with different phenols.

The structure elucidation of the new compounds was supported by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR in addition to mass spectra.

Additionally, a brief account on the docking study was explained through the binding conformation in comparison with the cytotoxic activity. Also, a brief account on the cytotoxic activity was explained.

The fourth chapter consists of the experimental part of this work which contains the detailed procedures used for the synthesis of the starting materials **Ia-b** and **VI**, the intermediates **IIa-b**, **IIIa-b** and **XIII** the target final compounds **IVa-i**, **V**, **VIIa-e**, **VIIIa-e**, **IX**, **X**, **XI**, **XIIIa-c**, **XIV**, **XV** and **XVIa-c**.

In addition, data obtained from the element and spectral analyses as well as their physical properties are given in this chapter. It also sheds the light on the anticancer activity in experiment 1, twenty-four compounds of newly synthesized derivatives compared with 2-(4-aminophenyl)benzothiazole (**19**) as a standard cytotoxic agent against (MCF-7) cell line. Compound **XVIc** exhibited the highest cytotoxic activity with IC_{50} 12.47 μ M, while in experiment 2, seven compounds of newly synthesized derivatives compared with 2-(4-aminophenyl)benzothiazole (**19**) as a standard cytotoxic agent against (MCF-7) and (A549) cell lines. Compound **IVc** exhibited the highest

cytotoxic activity with IC_{50} 13.25 μ M and 12.08 μ M against (MCF-7) and (A549) cell lines respectively.

This chapter also clarifies the correlation between the results of molecular docking and the anticancer activity.