Synthesis of substituted benzothiazole and benzoxazole derivatives of antitumor activity

Thesis presented by

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Abstract

This thesis comprises four chapters: the first one is an introduction which consists of a brief survey about different routes to synthesize 2-substituted benzothiazoles and 2-substituted benzoxazoles in addition to an account on their cytotoxic activities.

The second chapter deals with the aim of the work and the Schemes for the preparation of starting materials and the target benzothiazole, benzoxazole, pyrazole, pyrimidine, quinazoline and benzotriazine containing compounds.

The third chapter clarifies the theoretical discussion of the experimental work for the preparation of the starting materials $\mathbf{I_{a\&b}}$ and $\mathbf{V_{a\&b}}$.

Reaction of $\mathbf{I_{a\&b}}$ with triethyl orthoformate and malononitrile afforded the key intermediates $\mathbf{II_{a\&b}}$ which upon cyclization with hydrazine hydrate yielded $\mathbf{III_{a\&b}}$. In addition, compound $\mathbf{II_a}$ was cyclised to give $\mathbf{IV_{a\&b}}$ through treatment with certain isothiocyanates.

Moreover, substitution of iodide in $\mathbf{V_{a\&b}}$ by a cyanide anion gave $\mathbf{VI_{a\&b}}$ from which $\mathbf{VII_{a\&b}}$, **VIII** and $\mathbf{IX_{a\&b}}$ were obtained using different acylating agents such as acetic anhydride, *p*-chlorobenzoyl chloride and chloroacetyl chloride**,** sequentially. As an extension, nucleophilic substitution of chloro derivatives of $\mathbf{IX_{a\&b}}$ with different

primary and/or secondary amines yielded **X_{a-d}**. Furthermore, hydrolysis of the cyano compounds **$VI_{a\&b}$** either in basic or acidic medium afforded the carboxylic acids **$XI_{a\&b}$** and the carboxamides **$XII_{a\&b}$**, respectively.

Formation of quinazoline ring was constructed by reacting **$VI_{a\&b}$** with different reagents like phenyl isothiocyanate, formamide and formic acid to obtain **$XIII_{a\&b}$**, **$XIV_{a\&b}$** and **$XV_{a\&b}$**, in the same order. Reaction of **$XV_{a\&b}$** with phosphorous oxychloride formed the chloro derivatives **$XVI_{a\&b}$**, which was subjected to nucleophilic substitution reaction by treatment with aromatic amines affording **$XVII_{a-c}$**. On the other hand, alkylation on pyrimidine nitrogen of **$XV_{a\&b}$** with different alkyl halides achieved **$XVIII_{a\&b}$**.

A variety of quinazoline derivatives **$XIX_{a\&b}$**, **XX_{a-d}** and **XXI_{a-d}** were formed *via* reacting **$XII_{a\&b}$** with carbon disulfide, aromatic aldehydes and certain isothiocyanates, respectively. Additionally, refluxing compounds **$XII_{a\&b}$** in acetic anhydride led to preparation of both oxazinone derivatives **$XXII_{a\&b}$** and pyrimidinone derivatives **$XXIII_{a\&b}$**. Moreover, reacting compounds **$XII_{a\&b}$** with cyclopentanone and cyclohexanone afforded **$XXIV_{a-d}$**. Finally, formation of benzotriazine derivatives **$XXV_{a\&b}$** was obtained by subjecting **$XII_{a\&b}$** to a diazotization condition.

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

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

The fourth chapter consists of the experimental part of this work which contains the detailed procedures used for the synthesis of the starting materials **$I_{a\&b}$** and **$V_{a\&b}$**, the intermedtiates **$II_{a\&b}$**,**$VI_{a\&b}$**, **$IX_{a\&b}$**, **$XII_{a\&b}$**, **$XV_{a\&b}$** and **$XVI_{a\&b}$**, in addition to the target final compounds **$III_{a\&b}$**, **$IV_{a\&b}$**, **$VII_{a\&b}$**, **VIII**, **X_{a-d}**, **$XI_{a\&b}$**, **$XIII_{a\&b}$**, **$XIV_{a\&b}$**, **$XVII_{a-c}$**, **$XVIII_{a\&b}$**, **$XIX_{a\&b}$**, **XX_{a-d}**, **XXI_{a-d}**, **$XXII_{a\&b}$**, **$XXIII_{a\&b}$**, **$XXIV_{a-d}$** and **$XXV_{a\&b}$**.

This chapter also includes the *in-vitro* anticancer activity of twenty-six compounds of newly synthesized derivatives compared to **I_b** as a standard and demonstrates the correlation between the results of the molecular docking study and anticancer evaluation.

There was some sort of constancy between the docking study prediction and the *in-vitro* biological cytotoxic evaluation. Compound **$XVII_c$** showed the highest energy score (-21.34 Kcal/mol) and exhibited the most potent *in-vitro* cytotoxic activity with IC_{50} equal to 0.009 µM, while compounds **XI_a** and **$XXIV_a$** showed intermediate energy scores (-16.79 to -15.75 Kcal/mol) and exhibited moderate *in-vitro* cytotoxic activity with IC_{50} 0.066 and 0.067 µM, respectively. On the other hand, **XXV_a** showed a weak energy score -15.46 and exhibited the least *in-vitro* cytotoxic activity with IC_{50} 0.074 µM.

رئيس قسم الكيمياء العضوية الصيدلية

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