Synthesis of The New Pyrazolo[3,4-*d*]Pyrimidine Derivatives of Expected Antitumor Activity

Thesis presented by

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Master of Pharmaceutical Sciences (Organic Chemistry)

Cairo University (2009)

Submitted for The Degree of

The Doctor of Philosophy in Pharmaceutical Sciences

(Pharmaceutical Organic Chemistry)

Beni-Suef University

Abstract

This thesis comprises four chapters. The first one is an introduction which consists of a brief survey of cytotoxic activity of compounds containing pyrazolo[3,4-*d*]pyrimidine nucleus and the new approaches in their synthesis.

The second chapter deals with the aim of the work and the Schemes for the preparation of starting materials and the new required pyrazolopyrimidine containing compounds.

The third chapter clarifies the theoretical discussion of the experimental work for the preparation of the starting materials $\mathbf{I_{a-d}}$- **III**.

Compound **III** was cyclized either through the reaction with hydrazine hydrate or stirring with different primary amines to afford **IV** and $\mathbf{V_{a-c}}$, sequentially.

On the other hand, acid hydrolysis of **II** yielded **VI**. Reacting **VI** with diethylmalonate afforded 6-ethoxycarbonylmethylpyrazolopyrimidine derivative **VII**. Hydrazinolysis of **VII** gave the acid hydrazide **VIII**.

Moreover, compound **VI** was cyclized to give pyrazolopyrimidine derivative **IX** using chloroacetyl chloride.

Formation of pyrazole ring at position 4 in pyrazolopyrimidine system in compounds **X_{a-d}** and **XI** was prepared from compound **IV**. The reaction of **IV** with ethyl acetoacetate or different aromatic aldehydes afforded **XII** and **$XIII_{a-d}$**, respectively.

On the other hand, compound **V_b** was reacted with formic acid, acetic anhydride or ethoxymethylenemalononitrile and/or ethoxyethylidenemalononitrile giving **$XIV_{a\&b}$**.

Also, compounds **XV_{a-e}**, **$XVI_{a\&b}$**, **XVII**, **XVIII**, **XIX**, **XX**, **XXI** and **XXII** were synthesized from the reaction of **V_b** with different aromatic aldehydes , isothiocyanate derivatives, diethyloxalate, diethylmalonate, chloroacetyl chloride, ethyl cyanoacetate, sodium nitrite and oxalyl chloride, sequentially.

Moreover, reacting the acid hydrazide **VIII** with different aromatic aldehyds and carbon disulfide afforded **$XXIII_{a-e}$** and **XXIV**, respectively. Reaction of **XXIV** with different alkylating agents afforded **XXV_{a-d}**, while reacting **XXIV** with hydrazine hydrate gave **XXVI**. Also, compound **VIII** was subjected to diazotization conditions to yield **XXVII**. Phthalimido derivative **XXVIII** was obtained upon reacting **VIII** with phthalic anhydride.

Additionally, reaction of **VIII** with Phenyl isothiocyanate afforded **XXIX**. Cyclization of **XXIX** either in acidic medium or under basic condition yielded **XXX** and **XXXI**, respectively. While, **XXXII** was obtained from the reaction of **VIII** and ethyl isothiocyanate. The reaction of **VIII** with arylidene derivatives gave the unexpected products **$XXXIII_{a-c}$**.

Compound **IX** was subjected to nucleophilic substitution reactions to afford compounds **$XXXIV_{a-d}$** from which **$XXXV_{a-d}$** were prepared. Also **$XXXVI_{a-c}$** and **$XXXVII_{a-c}$** were prepared from **IX**. Alkylation of compound **IX** was occurred to yield **$XXXVIII_{a\&b}$**. Substitution of chlorine atom in **IX** with thiol group in **XXXIX**, then alkylating the thiol group with different alkylating agents or chloroacetanilide derivatives yielded **$XXXX_{a\&b}$** and **$XXXXI_{a\&b}$**, respectively.

The structure elucidation of the new compounds was supported by element analyses, IR, ^{1}H NMR, ^{13}C H NMR in addition to mass spectral data.

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

The fourth chapter consists of the experimental part of this work which contains the detailed procedures used for the synthesis of the starting compounds **I_{a-d}-III**, the intermediates **IV**,**V_b** and **VI-IX,** in addition to the target new pyrazolopyrimidine compounds **$V_{a\&c}$**, **X_{a-d}-$XIII_{a-d}$** and **XV_{b-e}-$XXXXI_{a\&b}$**, in addition to physical properties and detailed data obtained from element and spectral analysis of these compounds. It also includes the *in-vitro* anticancer activity of thirty-nine compounds of newly synthesized derivatives compared with methotrexate as a standard cytotoxic agent. Compounds **$XXXIV_b$**, **$XXXVIII_a$**, **$XXXX_b$** and **$XXXXI_{a\&b}$** showed the highest *in-vitro* cytotoxic activity. This chapter also demonstrates the correlation between the results of molecular docking study and the anticancer evaluation. There was some sort of consistency between the docking studies prediction and the *in-vitro* biological cytotoxic evaluation.

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