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# METHODS FOR SYNTHESIS OF SOME ANTI-CANCER CONJUGATED AMINO ACIDS (A REVIEW)

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## ABSTRACT

Purines are an important group of organic compounds where several compounds containing a purine residue are known to possess useful biological activity and used as antibacterial, antifungal and antitumor agents. These pharmacological properties of purines aroused our interest in synthesizing several new 6-mercaptopurine (6-MP) derivatives linked to amino acid via peptide bond with expected biological activity. 6-MP was S-alkylated by the methyl bromoacetate and then hydrolyzed with an alkaline sodium hydroxide solution to librate the free carboxylic group side chain. Also the alkylated 6-MP reacted with hydrazine hydrate to get hydrazide of 6-MP. Conventional solution method for peptide synthesis used as a coupling method between the free carboxyl and amine groups. The proposed analogues were successfully synthesized and their structural formulas were consistent with the proposed structures as they were characterized and proved by thin layer chromatography (TLC), melting point, infrared spectroscopy (IR) and elemental microanalysis.

**KEYWORDS:** mercaptopurine, methyl bromoacetate, antitumor agents.

## INTRODUCTION

Purines are an important group of nitrogen-containing compounds that are present in all forms of plant and animal life and play a vital role in biological processes. The quantity of naturally occurring purines produced on earth is huge, fifty percent (50%) of the bases in nucleic acids, adenine and guanine which are purines.[1] They serve as the source of cellular energy in ATP and together with pyrimidine, are the building blocks of DNA and RNA, two of the four deoxyribonucleotides and two of the four ribonucleotide which are purines (the

respective building blocks of DNA and RNA).[2,5] Purines also participate in the structure of the co-enzymes (e.g. NAD+, NADP+ and FAD) and they are involved in membrane signal transduction, translation and protein synthesis (GTP, cAMP, cGMP, RNA).[6]

Due to their similarity with cell components, purine analogues may act as substrates or inhibitors of enzymes of purine metabolism or as agonists/antagonists/inhibitors of adenosine receptors and protein kinases. This is particularly relevant in the development of antiparasitic chemotherapies, since most parasites rely heavily on purine salvage pathways as they cannot synthesize them de novo. As a result, a number of pharmacologically active purine analogues have been approved for their clinical application as chemotherapeutic agents such as 6-thioguanine (6- TG), 6-MP and AZT. In addition, it can be found as a nucleobase in some synthetic nucleoside analogues which are structurally similar to natural nucleosides. Many of these nucleoside analogues have antiviral and antitumor properties.[7,8]

## MATERIALS AND METHODS

Methods of Identification General Methods were used for purification and identification of the synthesized analogues including: Thin Layer Chromatography: Ascending thin layer chromatography was run for monitoring the reaction progress as well as checking the purity of our products. The compounds were revealed by reactivity with iodine vapor. • Melting Points: Electronic Melting Point Apparatus was used to determine all melting points reported in this work. • Infrared Spectra: Determinations of infrared spectra were recorded by KBr film FTIR shimadzu (Japan). • Elemental Microanalysis: Elemental microanalysis was done at the College of Science, Al-Mustansiriya University. It has been done using Euro-vector EA 3000A (Italy).

### Synthesis Esterification of amino acid Synthesis of L-methionine methyl ester HCl (Met-O-Me HCl), Compound A

A suspension of L-methionine (7.46 g , 50 mmol) dissolved in (100 ml) of absolute methanol, was cooled down to - 10 0C, then thionyl chloride (50mmol, 3.63 ml) was added drop wise (the temperature should be keep below –10 0C, the reaction mixture was left at 40 0C for 3h, then refluxed for 3h and left at room temperature overnight. The solvent was evaporated to dryness under vacuum, re-dissolved in methanol and evaporated, this process was repeated several times and re-crystallize the product from methanol-diethyl ether.[9] Percent yield, physical appearance, m.p and Rf values were appears high.

**Alkylationof 6-mercaptopurine, compound (B1)**

To a suspension of 2-mercaptopurine (2 g, 13 mmol) in 75 ml distilled water in 150 ml round bottom flask add triethyl amine liquid (1.81 ml, 13 mmol) dropwise in 5 min with stirring to get clear solution. Then methyl bromoacetate (1.23 ml, 13 mmol) added dropwise in 30 min at room temperature and continue stirring at room temperature for additional 1h. White precipitate was formed which filtered off, washed with water and recrystallized by ethanol:water (60:40).[10]

**Synthesis (7H-Purin-6-ylsulfanyl)-acetic acid, compound (B2**)

compound B1(2 gm, 8.919 mmole) dissolved in 20 ml of 20% sodium hydroxide solution in round bottom flask 100 ml with 2- 3 boiling chips and boil the solution under reflex for 1 h, then cool solution to room temperature, filter and acidify it to pH 5 with 5 M HCl solution and cool the mixture in ice bath, white precipitate formed which filtered, washed with water.[11]

Percent yield, physical appearance, m.p and Rf values were appears low.

**Synthesis of (9H-Purin-6-ylsulfanyl)-acetic acid hydrazide, compound (B3)**

compound B1 (2.242 g,10.0 mmol ) dissolved in 60 mL absolute ethanol, then hydrazine hydrate (1.2 mL, 25 mmol) was added. The reaction mixture was refluxed for 4 hours. Reaction was monitored by TLC. After the completion of reaction, solution was concentrated and refrigerated overnight. White precipitates obtained on cooling, were dried and recrystallized in ethanol.[12]

**Synthesis of 4-Methylsulfanyl-2-[2-(9H-purin-6-ylsulfanyl)-acetylamino]-butyric acid methyl ester, compound**

To a stirred solution of L-methionine Me ester HCl (comp. A) (0.998 g, 5 mmol) in 10 ml dry DMF, NMM (1.1 ml, 10 mmol) was added with stirring for 10 min. Compound B2 (1.05 g, 5 mmol) in 10 ml dry DMF was also added to the reaction mixture which was cooled down to -10 0C then HOBt (0.675 g, 5 mmol) and DCC (1.03 g, 5 mmol) were added with stirring, continue stirring for 2 days at 0 0C and then at room temperature for 5 days. At the end of reaction, DCU was filtered off and washed with DMF. The filterate was evaporated to dryness and re-dissolved in cold DMF, the excess of DCU which that still adhesive on the peptide residue was precipitated out filtered off, this process was repeated several times then the clear filtrate concentrated and dissolved in chloroform (100 ml), transferred to seperatory

funnel washed 3 times with 10 ml of 0.1N HCl solution, 3 times with 10 ml of 5% NaHCO3 solution, once with water and once with 10 ml of saturated NaCl solution. The ethylacetate layer was dried using anhydrous magnesium sulfate powder and evaporated under vacuum; the resulted product was collected, recrystallized from chloroform and n-hexane, dried in vacuum oven at 60 0C for 4 h.

**Synthesis of (2-(4-Hydroxy-phenyl)-1-{N'-[2-(9H-purin-6-ylsulfanyl)-acetyl]-hydrazinocarbonyl}-ethyl)-carbamic acid tert-butyl ester**

To a stirred solution of compound B3 (0.876 g, 3.91 mmol) in 10 ml dry DMF, NMM (0.42 ml, 3.9 mmol) was added with stirring for 10 min. Boc-tyrosine (1.09 g, 3.9 mmol) in 10 ml dry DMF was also added to the reaction mixture which was cooled down to -10ºC then HOBt (0.528 g, 3.91 mmol) and DCC (0.806 g, 3.9 mmol) were added with stirring, continue stirring for 2 days at 0 0C and then at room temperature for 5 days. The crude product was evaporated to exclude DMF and the filterate was evaporated to dryness and re-dissolved in cold DMF, the excess DCU which that still adhesive on the peptide residue was precipitated out filtered off, this process was repeated several times, then evaporate the filtrate to get clear oily residue that mixed with cold 5% NaHCO3 forming a white precipitate which was filtered and washed with cold 0.2 N HCl solution and excess of water. The resulted product was collected and recrystallized by (ethanol:water)(60:40), dried in vacuum oven at 60 0C for 4 h.

## CONCLUSION

The proposed compounds were successfully synthesized by the conventional solution method as previously described and their structure formula were consistent with the proposed structures since conformity of their structures was achieved by using the following techniques: thin layer chromatography (TLC), melting point, infrared spectroscopy (IR) and elemental microanalysis (CHNS).

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