Mansoura University  
Faculty of Pharmacy  
Department of Medicinal Chemistry

DESIGN AND SYNTHESIS OF CERTAIN  
BENZIMIDAZOLE DERIVATIVES AS POTENTIAL  
ANTINEOPLASTIC AGENTS

Thesis Presented By  
Ahmed Abu-Bakr Mohamed Salem  
B. Pharm. Sci., Mansoura University 2008

A thesis submitted in partial fulfillment of  
The Master Degree in Pharmaceutical Sciences  
(Medicinal Chemistry)

Supervisors  
Prof. Dr.  
Said M. Bayomi  
Professor of Med. Chemistry  
Faculty of Pharmacy  
Mansoura University

Dr.  
Azza R. Maarouf  
Assistant Professor of Med. Chemistry  
Faculty of Pharmacy  
Mansoura University

Dr.  
Naglaa I. Abdel-Aziz  
Assistant Professor of Med. Chemistry  
Faculty of Pharmacy  
Mansoura University

2013
Abstract

Several publications were pointed towards the antineoplastic activity of benzimidazole derivatives. These observations prompted the design and synthesis of the prepared compounds. Therefore, the present work describes the synthesis of 1-(1H-benzimidazol-2-yl)-3-(substituted aryl)prop-2-en-1-ones (Va-f) (scheme 1) and a series of 2-mercapto-1H-benzimidazole derivatives with attached tetrazolyl moiety VII, VIII, IX, X and XI (scheme 2). In addition, 1-[1-{2-(4-substitutedphenyl)-2-oxoethyl}-1H-benzimidazol-2-yl]-3-arylprop-2-en-1-ones (XIIIa-j) that were used as key intermediates for the preparation of several (1-(2-arylvinyl)-3-(4-substituted phenyl) pyrazino[1,2-a]benzimidazole derivatives (XIVa-j) (scheme 3) were synthesized and all the newly prepared compounds were subjected to anticancer screening. The contents of the present thesis are divided into 7 parts, in addition to the Arabic summary.

Part 1 is an introductory part that discusses carcinogenesis and different classes of anticancer agents according to their mechanisms of action in addition to various benzimidazole and chalcone derivatives involved in treatment of different types of cancer.

Part 2 includes the research objectives and the major aims that direct the theoretical and practical work.
Part 3 contains the theoretical discussion of the experimental work. It discusses the different possible conditions for the preparation of the desired compounds with a summarized data about the confirmation of these new compounds.

Part 4 represents the experimental part that discusses different methods and conditions that were used in this thesis for preparation of either the intermediate or final products. Moreover, the microanalytical and spectral data that confirm the structures of the newly synthesized compounds were summarized in this part.

The following new final compounds (31 compounds) were prepared in the present work:

1) 1-(1H-Benzimidazol-2-yl)-3-(substituted aryl) prop-2-en-1-ones (Va-f).
2) 2-(1-Phenyl-1H-tetrazol-5-ylthio)-1H-benzimidazole (VII).
3) Ethyl-3-[2-(1-phenyl-1H-tetrazol-5-ylthio)-1H-benzimidazol-1-yl]propanoate (VIII).
4) 3-[2-(1-Phenyl-1H-tetrazol-5-ylthio)-1H-benzimidazol-1-yl]propanoic acid hydrazide (IX).
5) 5-[2-[2-(1-Phenyl-1H-tetrazol-5-ylthio)-1H-benzimidazol-1-yl]ethyl]-1,3,4-oxadiazole-2-thiol (X).
6) 4-Phenyl-5-[2-[2-(1-phenyl-1H-tetrazol-5-ylthio)-1H-benzimidazol-1-yl]ethyl]-4H-1,2,4-triazole-3-thiol (XI).
7) 1-\{1-[2-(4-Substituted phenyl)-2-oxoethyl]-1\textit{H}-benzimidazol-2-yl\}-3-arylprop-2-en-1-ones \textbf{(XIIIa-j)}.

8) 1-(2-Arylvinyl)-3-(4-substituted phenyl)pyrazino[1,2-a]benzimidazoles \textbf{(XIVa-j)}.

The following starting materials and intermediates \textbf{(3 compounds)} were prepared in the work:

1) 2-(1-Hydroxyethyl)-1\textit{H}-benzimidazole \textbf{(II)}.
2) 2-Acetyl-1\textit{H}-benzimidazole \textbf{(III)}.
3) 2-Mercapto-1\textit{H}-benzimidazole \textbf{(VI)}.

\textbf{Part 5} represents the anticancer screening section which shades light on the antineoplastic activity of the compounds under investigation.

\textbf{Part 6} includes molecular modeling study of the newly synthesized compounds.

\textbf{Part 7} includes the list of \textbf{258} references and periodical literatures used in this thesis, covered the period of \textbf{1887-2013}. 