

# **STUDIES ON THE SYNTHESIS OF CONDENSED HETEROCYCLO-BENZIMIDAZOLES**

**A Thesis**

Submitted to Faculty of Science, Cairo University, Fayoum Branch in  
Partial Fulfillment of the Requirements of the Degree of Master of  
Science in Organic Chemistry

**By**

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**Title: Studies on the Synthesis of Condensed Heterocyclo-  
Benzimidazoles**

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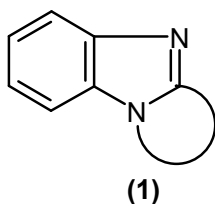
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## **SUMMARY**

Great efforts have been directed towards the synthesis of condensed heterocyclo-benzimidazoles **1** as a result of their multifarious biological activities.



The Candidate's work deals with the synthesis of various types of this class of compounds namely: imidazo[1,5-*a*]benzimidazoles; 1,3-thiazolo[3,2-*a*]benzimidazoles; pyrazino[1,2-*a*]benzimidazoles ; 1,4-thiazino[4,3-*a*]benzimidazoles; 1,2,4-triazino[4,5-*a*]benzimidazoles; and benzimidazo[2,1-*c*]1,4-benzodiazepine. Hence, the introductory chapter (Chapter 1) of the thesis was devoted to review the synthesis of different condensed heterocyclo-benzimidazole systems.

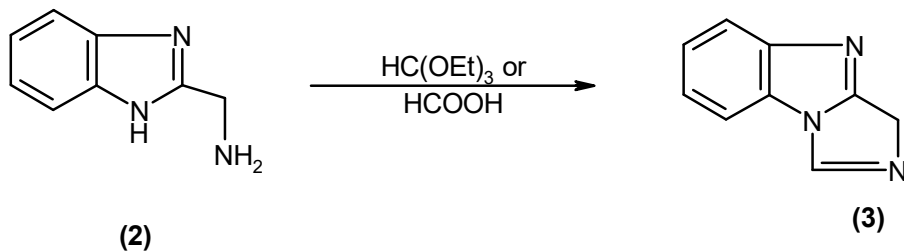
In chapter 2, the candidate discusses the results of his own work on the aforementioned condensed heterocyclo-benzimidazoles.

### **I) Synthesis of imidazo[1,5-*a*]benzimidazoles.**

#### **A) Imidazo[1,5-*a*]benzimidazole :**

Two reactions were used for the synthesis of unsubstituted imidazo[1,5-*a*]benzimidazole **3** comprising:

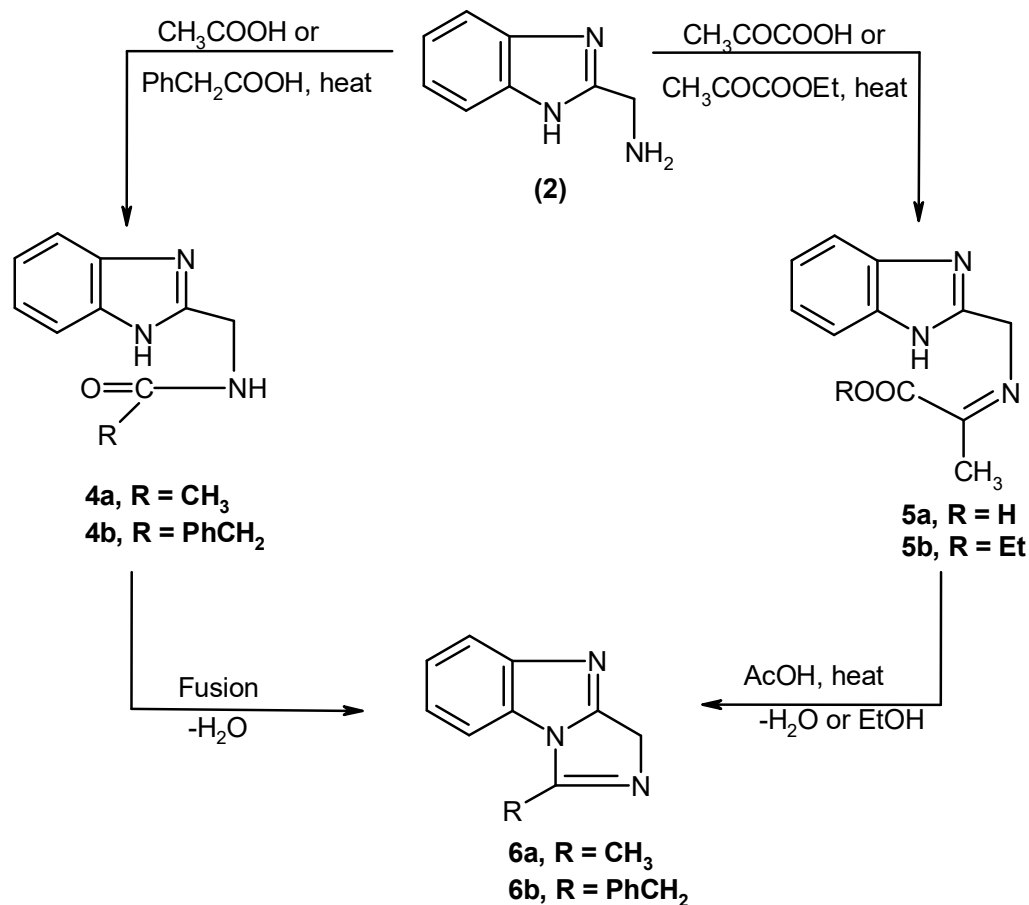
1. Reaction of 2-aminomethylbenzimidazole (**2**) with triethyl orthoformate.
2. Reaction of **2** with formic acid.



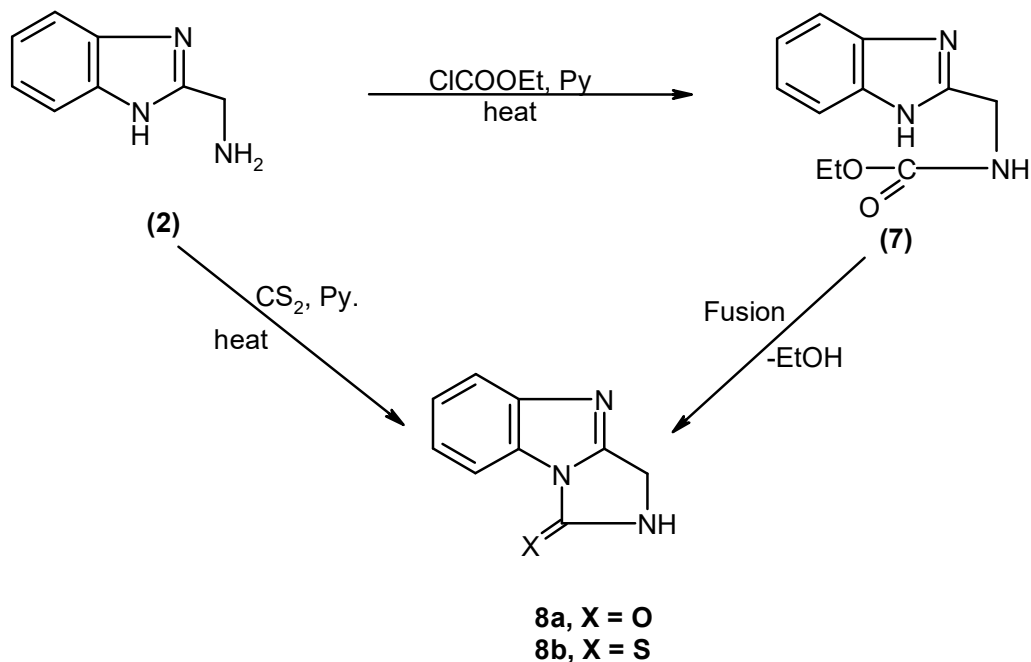
### B) 1-substituted-imidazo[1,5-*a*]benzimidazoles:

Six synthetic approaches were used for the synthesis of 1-substituted imidazo[1,5-*a*]benzimidazoles.

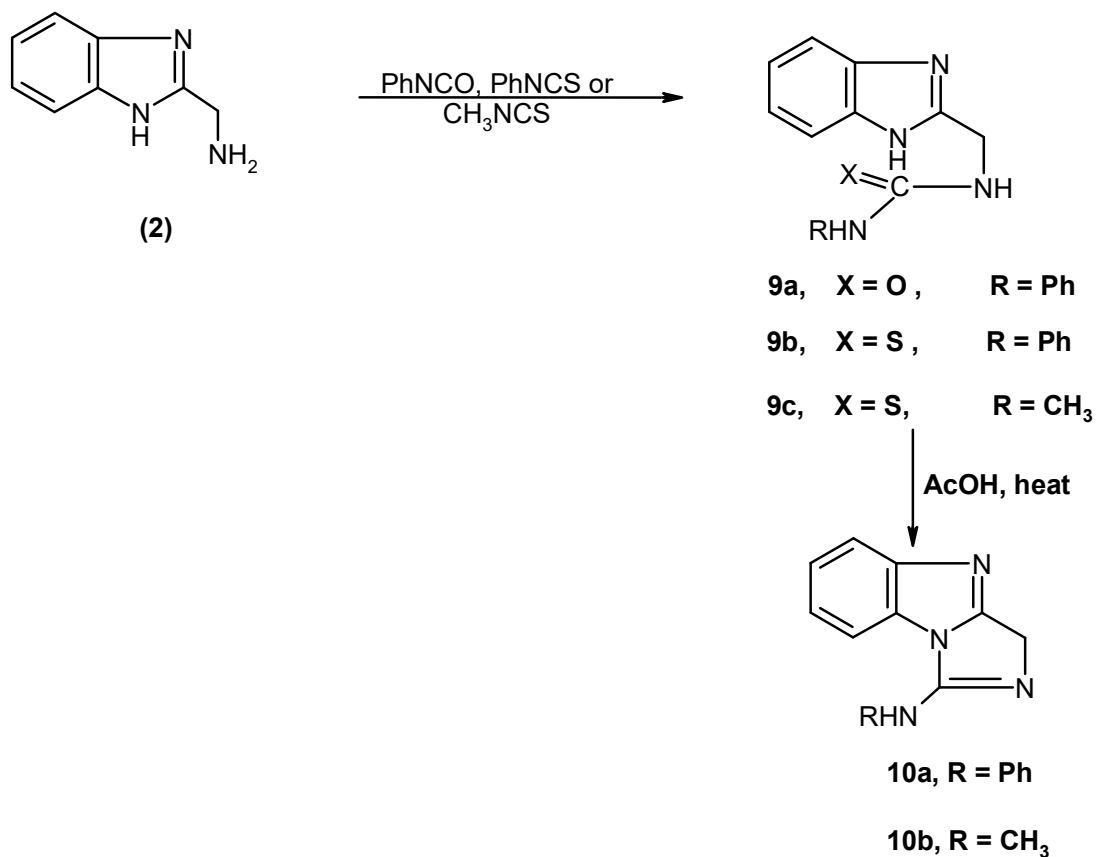
1. Reaction of **2** with acetic acid or phenylacetic acid gave the corresponding *N*-(benzimidazol-2-ylmethyl)-2-acetamides **4a,b** which effected by thermal dehydrative cyclization to give **6a,b**. Condensation of **2** with pyruvic acid or ethyl pyruvate afforded the imino intermediates **5a** and **5b**, respectively, which underwent acid-catalyzed dehydrative cyclization to give the same 1-methyl-3*H*-imidazo[1,5-*a*]benzimidazole (**6a**).



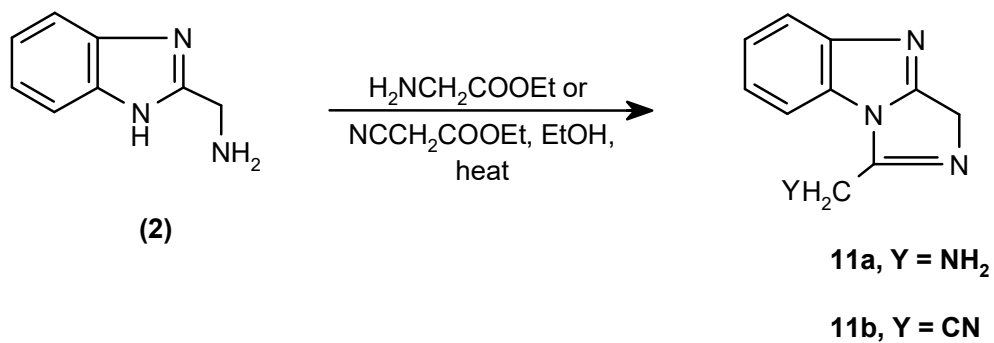
2. Condensation of compound **2** with ethyl chloroformate in boiling pyridine followed by thermal cyclization of the intermediate carbamic acid ethyl ester derivative **7** gave the 3*H*-imidazo[1,5-*a*]-benzimidazol-1(2*H*)-one (**8a**). The thio congener **8b** of **8a** was prepared through the reaction of **2** with carbon disulfide in pyridine.



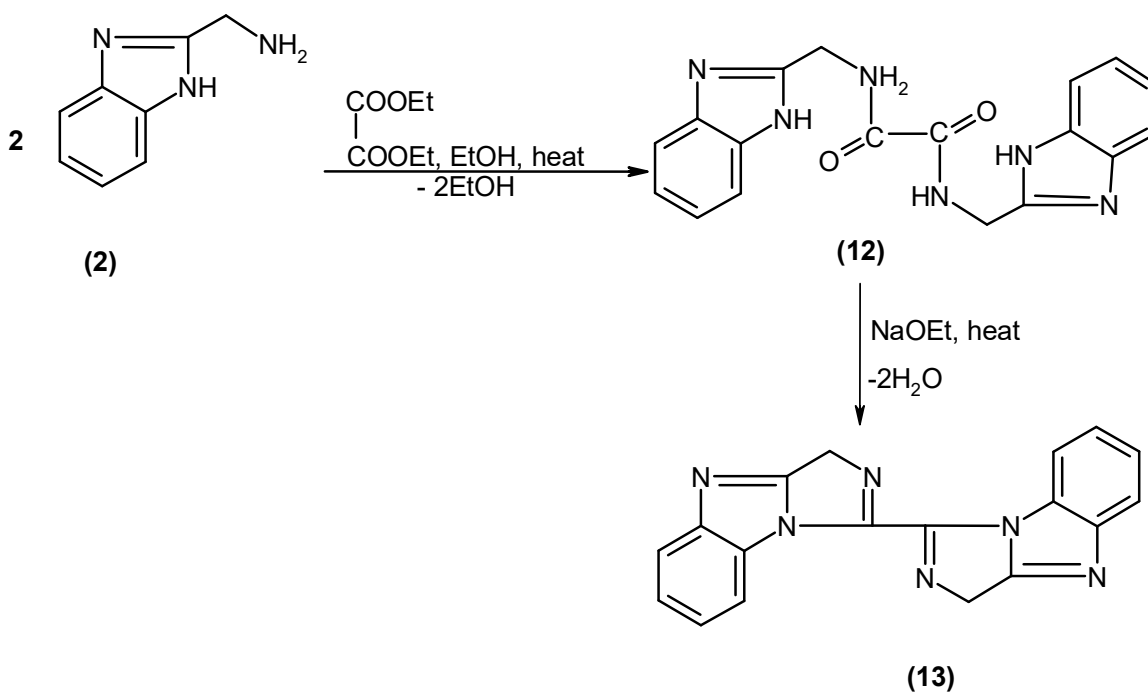
3. Coupling of compound **2** with phenyl isocyanate or phenyl isothiocyanate afforded the corresponding phenylurea **9a** or phenylthiourea **9b** derivatives which heterocyclized by heating with acetic acid to give one and the same 1-phenylamino-3*H*-imidazo[1,5-*a*]-benzimidazole (**10a**). The 1-methylamino congener **10b** of **10a** was similarly prepared.



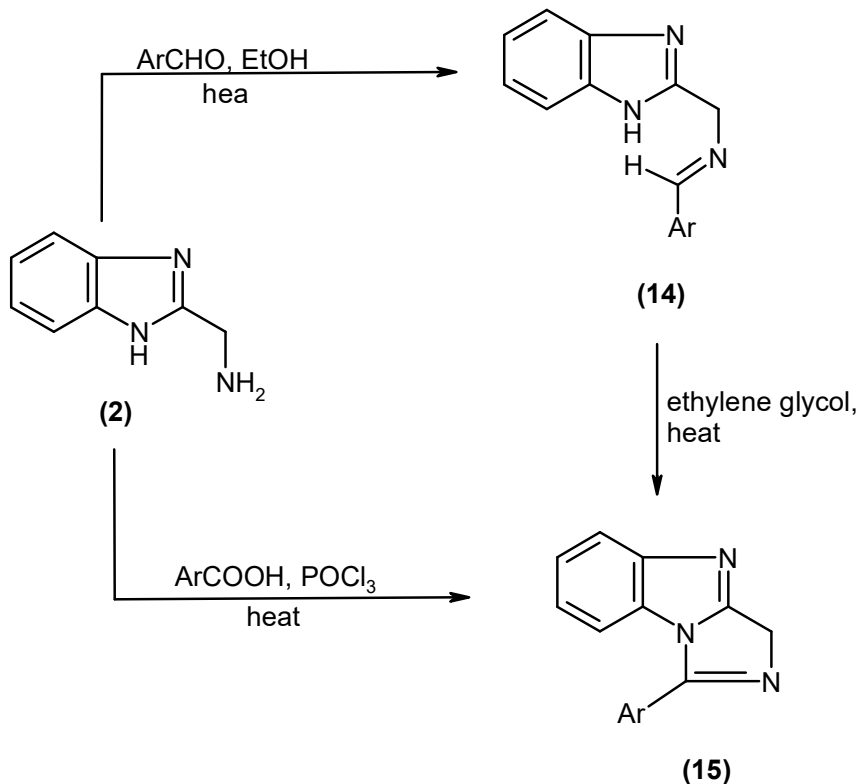
4. Ring closure of compound **2** with substituted ethylacetates, namely: ethyl aminoacetate (glycine ethyl ester) or ethyl cyanoacetate afforded the corresponding 1-substituted-methyl-3*H*-imidazo[1,5-*a*]-benzimidazoles **11a** and **11b**, respectively.



5. Reaction of amine compound **2** with diethyl oxalate (2:1) gave *N,N*-bis oxaloamide derivative **12** which then underwent dehydrative cyclization with sodium ethoxide to give bis-{3*H*-imidazo[1,5-*a*]-benzimidazol-1-yl} (**13**).



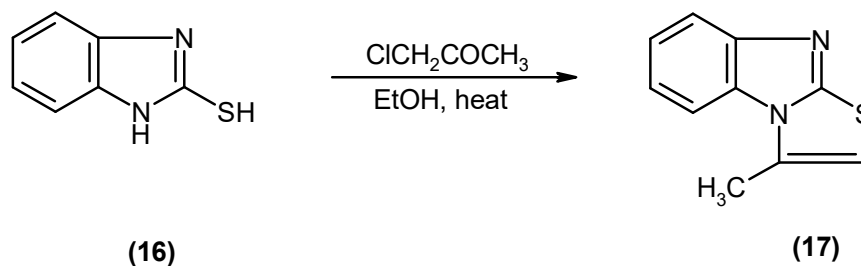
6. Condensation of compound **2** with aromatic aldehydes followed by dehydrogenative cyclization of the formed arylideneamino compounds **14** to give the 1-aryl-3*H*-imidazo[1,5-*a*]benzimidazoles **15**. The latter compounds were also obtained directly from **2** by the reaction with the appropriate carboxylic acids in the presence of phosphoryl chloride.



## II) Synthesis of 1,3-thiazolo[3,2-*a*]benzimidazoles:

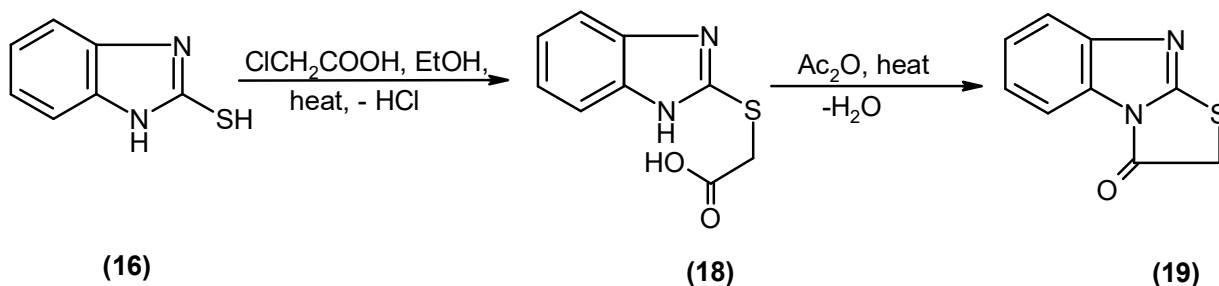
Two pathways were used for the synthesis of 1,3-thiazolo[3,2-*a*]benzimidazoles :

1. Heterocyclization of 2-mercaptobenzimidazole (16) with chloroacetone gave directly the 3-methyl-1,3-thiazolo[3,2-*a*]benzimidazole (17).





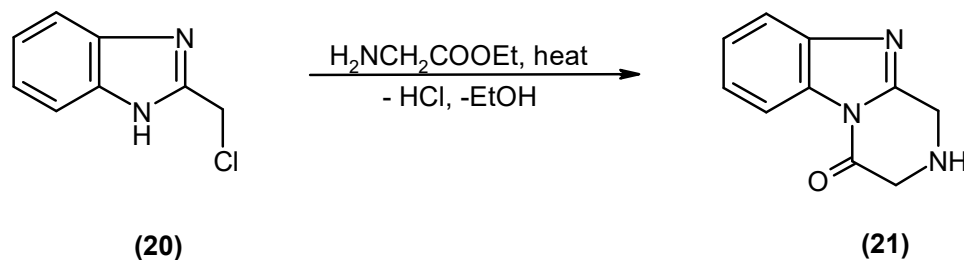
2. Reaction of mercapto compound **16** with chloroacetic acid afforded the intermediate mercaptoacetic acid derivative **18** which underwent dehydrocyclization to 1,3-thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one **19**.



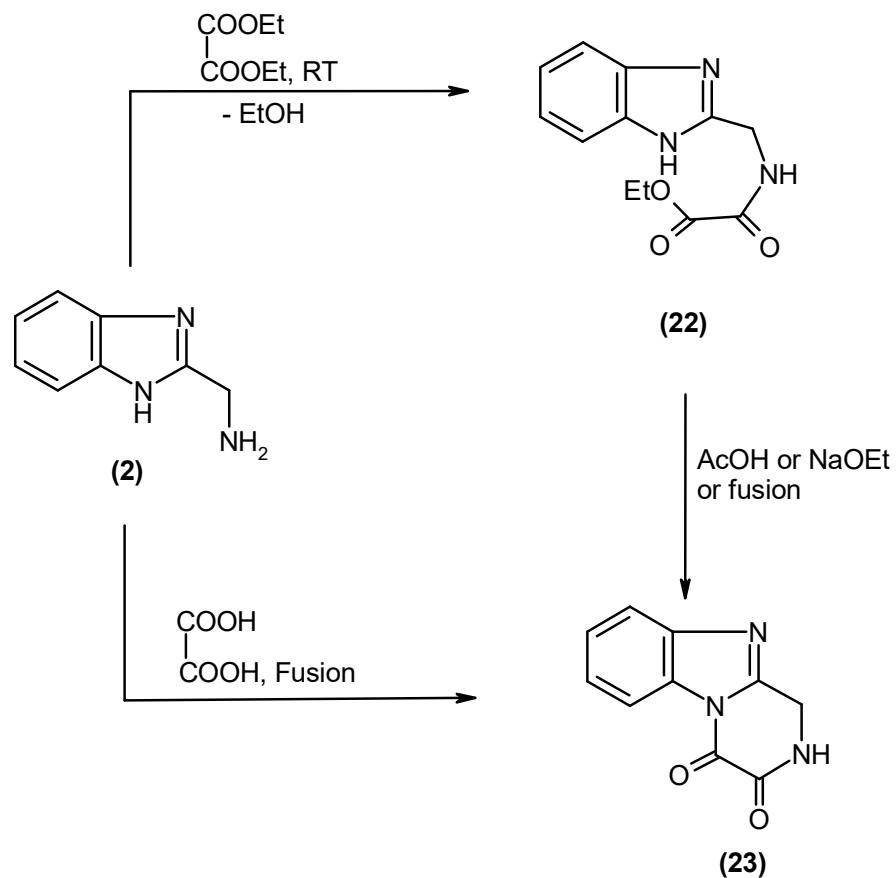
### III) Synthesis of pyrazino[1,2-*a*]benzimidazoles.

Two alternative routes were applied for the synthesis of pyrazino-[1,2-*a*]benzimidazoles.

1. Reaction of 2-chloromethylbenzimidazole (**20**) with glycine ethyl ester gave the 1,3-dihydro-pyrazino[1,2-*a*]benzimidazol-4(2*H*)-one (**21**).



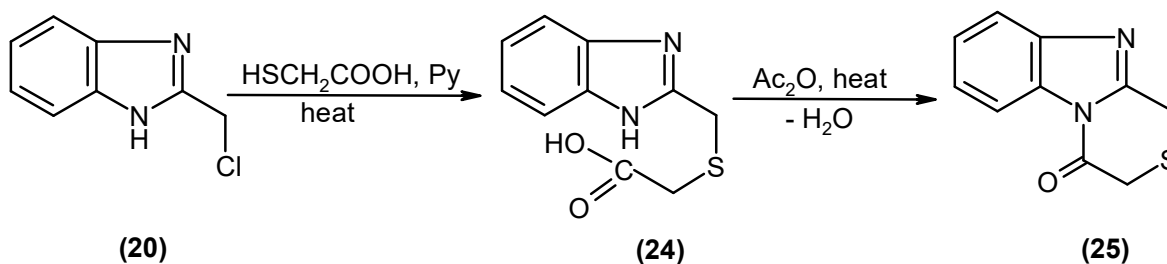
2. Reaction of compound **2** with diethyl oxalate (1:1) followed by acid-, base- or thermal-induced cyclization of the formed intermediate **22** gave the 1*H*-pyrazino[1,2-*a*]benzimidazol-3,4(2*H*)-dione (**23**). The latter compound was also obtained directly from fusion of **2** with oxalic acid.



#### IV) Synthesis of 1,4-thiazino[4,3-*a*]benzimidazole.

One synthetic method was used for the synthesis of the title compound.

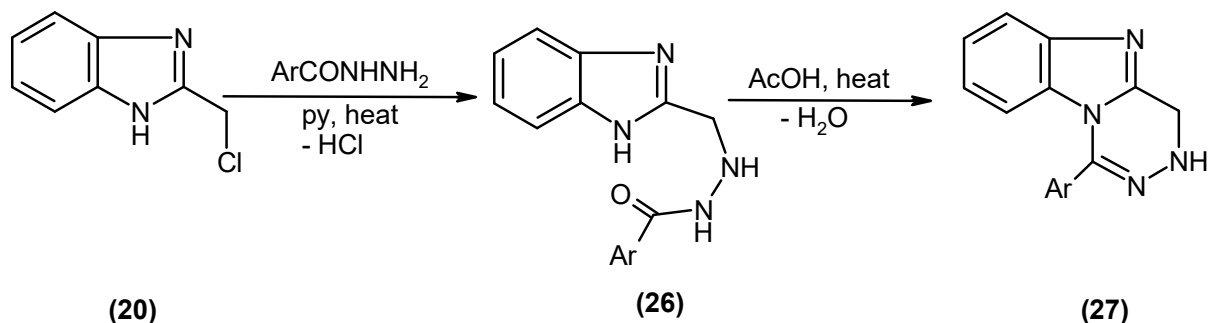
Condensation of 2-chloromethylbenzimidazole (20) with mercaptoacetic acid afforded the mercaptoacetic acid derivative 24 which dehydrocyclized to 1,3-dihydro-1,4-thiazino[4,3-*a*]benzimidazol-4-one (25).



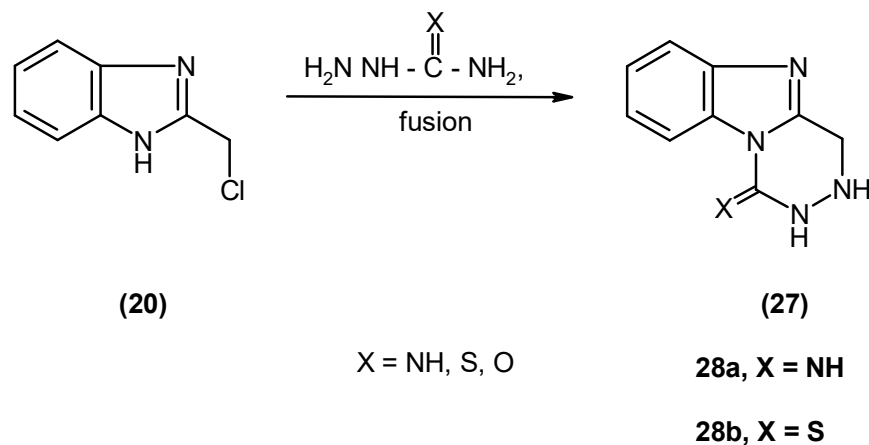
## V) Synthesis of 1,2,4-triazino[4,5-*a*]benzimidazoles.

Two different reaction pathways were used for the synthesis of the title compounds.

1. Condensation of 2-chloromethylbenzimidazole (**20**) with aromatic or heteryl acid hydrazides followed by dehydrative cyclization of the formed hydrazides **26** to give the 1-substituted-3,4-dihydro-1,2,4-triazino[4,5-*a*]benzimidazoles **27**.



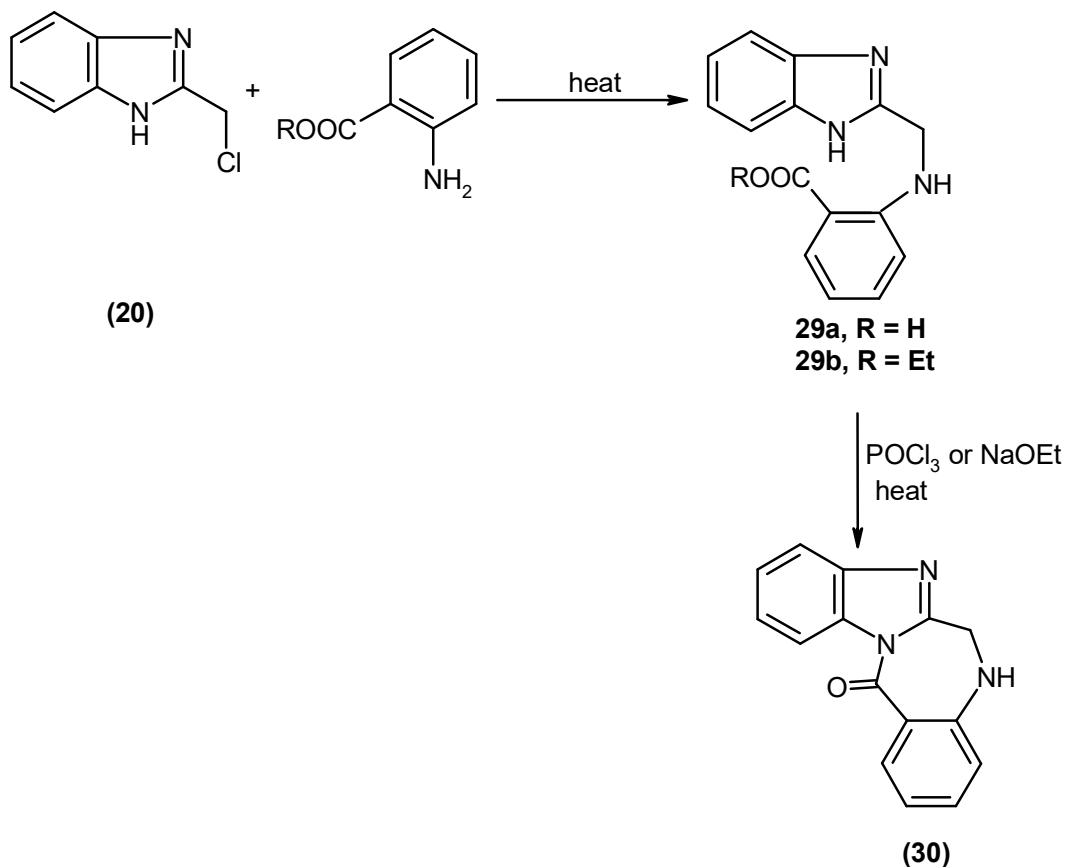
2. Reaction of compound **20** with aminoguanidine, thiosemicarbazide or semicarbazide furnished the corresponding 1-substituted-1,2,4-triazino[4,5-*a*]benzimidazoles **28a-c**.



## VI) Synthesis of benzimidazo[2,1-*c*]1,4-benzodiazepine.

One reaction path was used for the synthesis of the title compound.

Condensation of compound **20** with anthranilic acid or its ethyl ester gave intermediates **29a** or **29b** which upon heterocyclization afforded the same benzimidazo[2,1-*c*]1,4-benzodiazepine (**30**).



The structure of the prepared compounds were assigned on the basis of their molecular absorption spectra, proton magnetic resonance spectra, mass spectra as well as their elemental analysis data. Mechanistic pathways were proposed whenever feasible to explain how the products were formed.

Chapter 3 includes the experimental details of the Candidate's work as well as the physical constants and spectral properties of the prepared compounds.

The relevant references are compiled at the end of the thesis.