New Bisbenzimidazole-Chalcone Structures; Design, Synthesis, and Docking Studies

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Abstract

Cysteine cathepsins play an important role in various physiological and pathological processes such as tumor progression and metastasis, osteoporosis, osteoarthritis, and atherosclerosis. For this reason, it is thought that a cysteine cathepsin inhibitor can reduce tumor growth and metastasis. It has been reported in most studies that molecules bearing the chalcone structure show inhibitory activity against cathepsins.

In this study, a group of compounds with the bisbenzimidazole-chalcone structure were designed and synthesized. Docking studies of the compounds were also performed for Cat K and Cat L. As a result of docking studies, it was determined that the designed compounds (**EA-1**-**EA-16**) had better docking scores compared to the reference compound **8e**. The results showed that the compounds could potentially be anticancer-effect through the enzymes Cat K and Cat L.

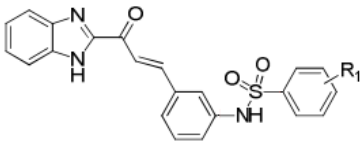
Keywords**:** *Bisbenzimidezole, chalcone, cathepsin, molecular docking, anticancer activity*

Introduction

The number of cancer patients and the development of new anticancer drugs with different targets are increasing rapidly around the world. Among these targets, cathepsin enzymes have attracted great interest in recent years. According to the active zone amino acids (cysteine; B, C, F, H, K, L, O, S, V, W, X, aspartic acid; D and E, serine; G) cateps divided into three subgroups are involved in numerous physiological process [1]. Many cysteine cathepsins, including cathepsin (Cat) B, F, H, L, K, S, V, and X, have been reported to play an important role in various physiological and pathological processes such as tumor progression and metastasis, osteoporosis, osteoarthritis, and atherosclerosis [2]. Increased regulation of Cat L has been reported in a wide variety of human malignancies, including cancers of the colon, breast, lung, melanoma and pancreas [3]. In addition, Cat K is overexpressed in melanoma, prostate cancer, giant cell tumors and basal cell carcinoma and has also been associated with breast cancer

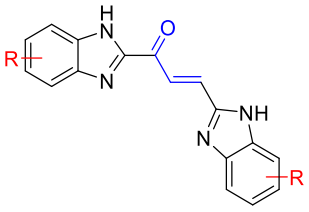
and osteosarcoma [4]. Therefore, the fact that a cysteine cathepsin inhibitor can reduce tumor growth and metastasis suggests that targeting cysteine cathepsins may be therapeutically beneficial [5]. Some compounds such as quinazoline, chalcone, pyrazoline, semicarbazone and thiosemicarbazone have activity against cathepsins [6-9]. Belonging to the flavonoid family, chalcones are open-chain molecules that carry an α, β-unsaturated carbonyl system between two aromatic rings and represent an important class of molecules abundant in edible plants [10]. Chalcones exhibit a variety of pharmacological effects, including anti-proliferative, anticancer, antioxidant, and anti-inflammatory activities [11]. Notable structures in the development of new drug research for cancer treatment include the benzimidazole ring system. In the literature, it has been observed that successful results have been obtained for benzimidazole derivatives used as active substances due to their different pharmacological effects.

Yali Wang et al. reported that a group of compounds (8a-8i) with benzimidazole-chalcone structure they synthesized showed antitumor activity by inhibiting Cat K and Cat L [13].



R_1; **8a**: 2-Cl **8b**: 3-Cl **8c**: 4-Cl **8d**: 2-CH_3 **8e**: 3-CH_3 **8f**: 4-CH_3 **8g**: 3,5-$(Cl)_2$ **8h**: 3,4-$(CH_3)_2$ **8i**: 3,5-$(CH_3)_2$

Based on this information, in this study, design, synthesis and molecular modeling studies of new compounds with bisbenzimidazole-chalcone structure were carried out (Scheme 1).



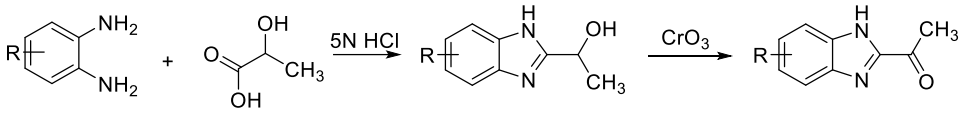
R= -H, -Cl, -CH_3, -NO_2

Scheme 1. Synthesis of Bisbenzimidazole-Chalcone Structures

Results and Discussion

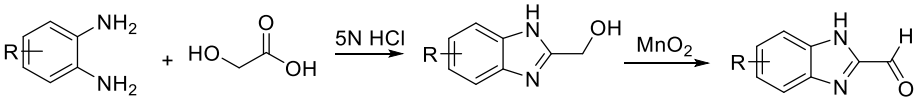
Chemistry

For compounds (**I**), it was obtained by the Philips method with substituted 1,2-phenylenediamine and lactic acid to be purchased commercially [14]. Then, by oxidation of the secondary alcohol compounds obtained with CrO_3, 2-acetylbenzimidazole derivative compounds (**II**) were obtained [15].



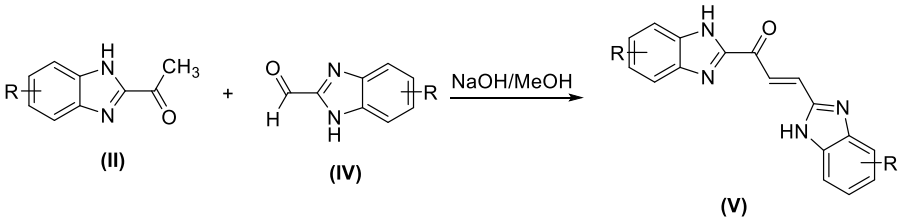
(I) (II)

2-hydroxymethylbenzimidazole derivatives (**III**) were synthesized by the reaction of commercially purchased substituted 1,2-phenylenediamine and glycolic acids by Philips method [14]. Then, benzimidazole-2-carbaldehyde derivatives (**IV**) were obtained as a result of oxidation of these synthesized derivatives with MnO_2 [16].



(III) (IV)

Bisbenzimidazole-chalcone derivative (**V**) compounds were obtained by Claisen-Schmitt condensation reaction of the synthesized compounds (**II**) and (**IV**) in methanol or ethanol in basic medium [17].



(II) (IV) (V)

R= H, Cl, CH_3, NO_2

Docking studies

Maestro 12.8 (Schrodinger, New York) program was used in all molecular docking studies. The ligands were minimized using LigPrep, a utility of Schrodinger. The X-ray structure of the possible target proteins (PDB ID: 1NLJ, 2XU3) was downloaded from the RCSB Protein Data

Bank (www.rcsb.org) [18] Schrödinger's modules, Protein Preparation Wizard Prime, Impact, Epik, Propka, and Prime were used for removing ligands and solvent molecules in protein, adding hydrogens, assigning charges and deleting polar hydrogens for clarity. Ligands were docked in this grid map 50 times in extra precision (SP) mode using the Glide software. [19] (Fig. 1 and Fig.2)

Bileşik No	Docking scores (PDB ID: 1NLJ) (CATHEPSIN K)	Bileşik No	Docking scores (PDB ID: 2XU3) (CATHEPSIN L)
EA-1	-6,907	**EA-1**	-4,660
EA-2	-6,185	**EA-2**	-4,630
EA-3	-6,689	**EA-3**	-4,882
EA-4	-5,190	**EA-4**	-4,378
EA-5	-5,586	**EA-5**	-5,025
EA-6	-5,073	**EA-6**	-5,264
EA-7	-5,198	**EA-7**	-5,117
EA-8	-5,079	**EA-8**	-4,693
EA-9	-5,277	**EA-9**	-3,686
EA-10	-6,329	**EA-10**	-5,246
EA-11	-5,892	**EA-11**	-5,303
EA-12	-5,390	**EA-12**	-4,873
EA-13	-2,933	**EA-13**	-4,297
EA-14	-4,289	**EA-14**	-4,089
EA-15	-5,041	**EA-15**	-3,591
EA-16	-5,127	**EA-16**	-4,111
2CA*	-6,813	**XU3***	-4,680
8e	-4,392	**8e**	-3,225

2CA: crystalline ligand, **XU3:** crystalline ligand, **8e:** most active compound in the reference article

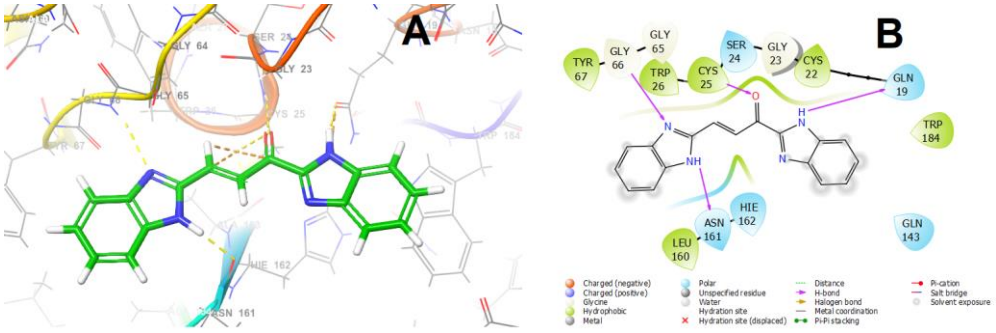


Figure 1. EA-1 docked pose in cathepsin K and ligand interactions. A) Docked pose for EA-1 in the active site cleft of human cathepsin K. B) Two-dimensional (2D) interactions of EA-1

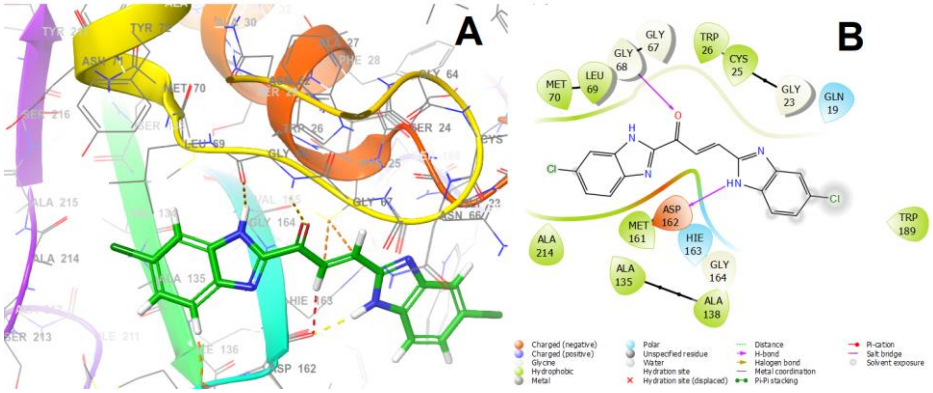


Figure 2. EA-11 docked pose in cathepsin L and ligand interactions. A) Docked pose for EA-11 in the active site cleft of cathepsin L. B) Two-dimensional (2D) interactions of EA-11

With the information obtained as a result of docking studies, it was determined that the synthesized compounds could have potential anticancer effects through Cat K and Cat L enzymes.

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