Antibacterial Activity Screening Of an Imine Compound Synthesized Using a Cinnamaldehyde Derivative Against *Staphylococcus Aureus* Strains

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Introduction and research aims

Cinnamaldehyde, a major constituent of cinnamon oil, is an aromatic compound with a benzene ring and an aldehyde group attached to an unsaturated C=C bond at both ends. Studies on cinnamaldehyde have shown that it exhibits a broad range of biological activities. Taking into account its organic nature and biological (antimicrobial, anticancer and so on) activity, cinnamaldehyde serves as an effective drug research platform. In addition, the US FDA has classified it as Generally Recognized as Safe (GRAS). Some investigated cinnamaldehyde derivatives became more appealing due to the presence of interesting and different functional groups. For example, the degree of oxidative stress that leads to chronic disease is decreased by the addition of methyl, halogen, and methoxy groups to the phenyl and aliphatic groups, which function as antioxidant agents; thus, these special structural features have the potential to be anticancer agents. Taking into account all the above mentioned, we decided to combine the advantages of cinnamaldehyde and azomethine moieties into one molecule in order to prepare a multipurpose biologically active compound. For this purpose, the synthesis of novel azomethines on the basis of cinnamaldehyde derivatives (2 trans-cinnamaldehyde, α-methyl-trans-cinnamaldehyde, 2-methoxy-trans-cinnamaldehyde and α-bromocinnamaldehyde) and heteroatom-contained aliphatic polyamines (tris(2-aminoethyl)amine and 2,2-(ethylenedioxy)bis(ethylamine) was performed by a condensation reaction in a non-catalyst medium. The benefit of this reaction is that it eliminates the requirement for a particular purification process, such as column chromatography, for the produced chemicals. The novel azomethine on the basis of trans-cinnamaldehyde and polyamine such as tris (2-aminoethyl) amine (F2-112B) was synthesized.

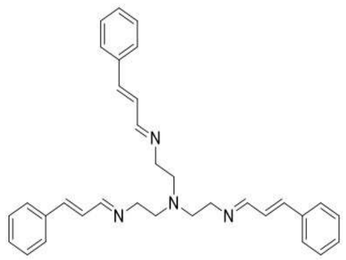
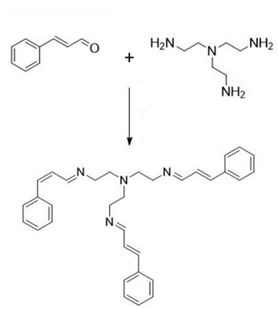
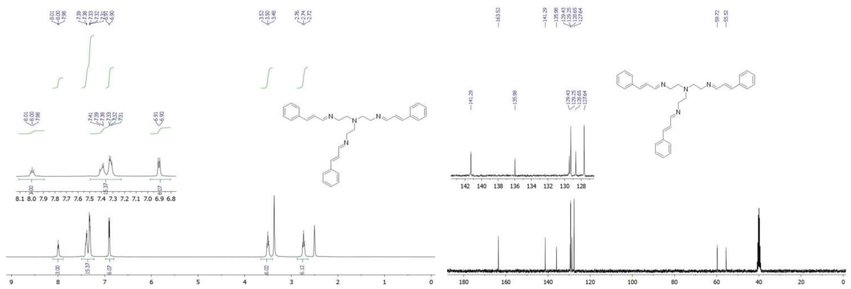


Figure 1. Compound F2-112B

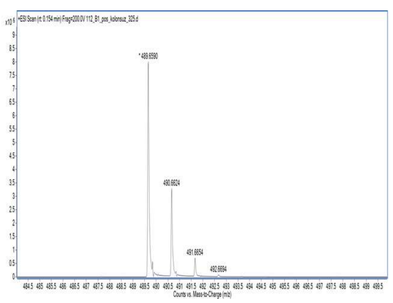
Methods



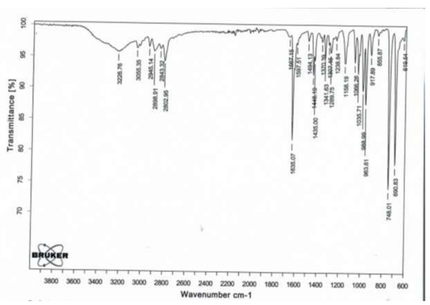
Synthesis scheme of compound F2



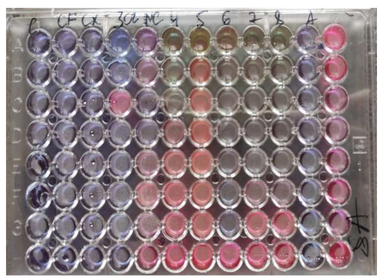
^{1}H and ^{13}C NMR spectra of synthesized MHC3



MALDI-MS spectrum of MHC3



Powder XRD of compound F2



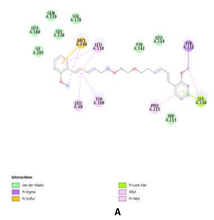
96-well microtiter antibacterial assay

Results

Cinnamaldehyde, as an example of a natural compound, is a beneficial drug research framework since it may be provided not only through the extraction of natural components but also through synthesis [74]. The natural source of cinnamaldehyde is an essential cinnamon oil, which is derived from the bark of Cinnamomum plants. Taking into account its organic nature and biological (antimicrobial, anticancer and so on) activity, cinnamaldehyde serves as an effective drug research platform. In addition, the US FDA has classified it as Generally Recognised as Safe (GRAS). Some investigated cinnamaldehyde derivatives became more appealing due to the presence of interesting and different functional groups. For example, the degree of oxidative stress that leads to chronic disease is decreased by the addition of methyl, halogen, and methoxy groups to the phenyl and aliphatic groups, which function as antioxidant agents; thus, these special structural features have the potential to be anticancer agentsThe compound was synthesized using a straightforward condensation reaction between trans-cinnamaldehyde, acetonitrile and tris(2-aminoethyl)amine. The positive side of the reaction is that it proceeds in a non-catalyst medium and no special purification method for the produced compounds, such as column chromatography, is required. The structure of compound was determined by 1H, 13C NMR spectroscopy, mass spectrometr, FTIR and elemental analysis. Imine pharmacophore groups offer the advantage of serving as the foundation for various drug representatives. Examples include furazolidone for bacterial or protozoal diarrhea, nitrofurantoin for uncomplicated urinary tract infections, and imbruvica for chronic lymphocytic leukemia and mantle cell lymphoma. Cinnamaldehyde, a major constituent of cinnamon oil, is an aromatic compound with a benzene ring and an aldehyde group attached to an unsaturated C=C bond at both ends. Studies on cinnamaldehyde have shown that it exhibits a broad range of biological activities. A novel imine compound, created using trans-cinnamaldehyde and polyamines such as tris (2-aminoethyl) amine (compound 5), was synthesized (table 1). The antibacterial activity of the compound was tested against clinical isolates (*S. aureus*, *S. aureus* ATCC 6538, *S. aureus* ATCC 25923, *S. aureus* UAMS-1, and S. aureus UAMS -929) using the two-fold microdilution method. The obtained results were compared with the results of the ampicillin and gentamicin. It was revealed that the MIC of F2-112B in the case of S. aureus (8 μg/mL) were lower than the MIC of ampicillin (16 μg/mL). The MIC value of compound F2-112B was equal (16 μg/ml) to ampicillin in the case of *S. aureus* ATCC 6538. According to the results, compared with other strains, compound 5 showed similar activities against UAMS-929 and ATCC 25923, and its MIC values were 64 μg/ml for each strain. The MIC value was 128 μg/ml when compound 5 was tested against the S. aureus strain UAMS-1. We also examined the potential binding mode between compound 5 and bacterially derived target proteins and carried out a protein–ligand docking simulation. The docking results for PBP2a (5M18) indicated that compound 5 successfully binds to the allosteric binding site of the protein, which aligns with the binding site of Cefepime (table 2), demonstrating a high binding affinity of -8.42 Kcal/mol.

Table 1. Minimum inhibitory concentration (in μg ml^{-1}) for compound F1-112B

Investigated compounds	Bacterial strains				
	S. aureus	*S. aureus* ATCC 6538	*S. aureus UAMS-1*	*S. aureus* UAMS-929	*S. aureus ATCC25923*
F2-112B	8	16	128	8	64
Ampicillin	16	16	32	32	16



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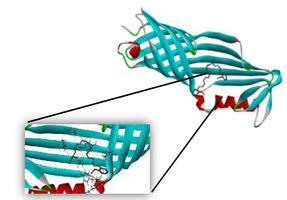

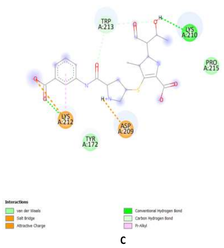

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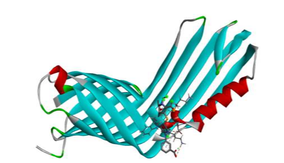
Table 2. Receptor binding domain, and bacteria are given in table

Bacteria related data					
Bacteria	Protein	PDB Code	Belong to receptor binding domain		
			x	y	z
Staphylococcus aureus	PBP3	3VSL	34.47	-51.95	2.06
	PBP2a	5M18	19.62	-17.89	-52.91



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Future Directions

- Synthesis novel compounds on the bases of cinnamaldehyde
- Study toxicity activity of the compounds against human immortalized keratinocyte cells (HaCaTs)
- Studying the mechanism action of compounds in *S. aureus*
- Studying anticancer activity of the compound

Conclusions

- F2-122B showed potential activity (MIC 8 μg ml^{-1}) in case *S. aureus.*
- PanK (4BFT) protein was identified as a target for synthesized compound F2-122B.
- The results of computational studies demonstrated that compound docking score is better than control

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