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Biological Evaluation of Aminoindane Derivatives as Antibacterial Agents

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Abstract

The aminoindane ring is the most studied skeletal structure in synthetic chemistry, in the synthesis of intermediates and because it is a biologically active molecule. Bioactive properties of the aminoindane ring include antibacterial, antiviral, antiapoptotic, antipyretic, analgesic, anticonvulsant, and antiparkinsonian activities. The most important bacteria in responsibility of nosocomial infections obtained in hospitals across the world are *Acinetobacter baumannii* and Methicillin-resistant *Staphylococcus aureus*. MRSA and *A. baumannii* have become resistant to numerous antibiotics. The development of novel antibiotic drugs is thus urgently needed. This study as investigated at the antibacterial effects of previously synthsized compounds **8** and **9** on *A. baumannii* and MRSA disease microorganisms. Studies on antibacterial activity employed disc diffusion and microdilution techniques. The investigation revealed that whereas the pathogenic organisms of compounds **8** and **9** formed zones that inhibited bacterial development, no zones formed in compounds **5**, **6**, and **7**. Compounds **8** and **9**'s zone diameters against *A. baumannii* and MRSA were estimated to be between 0.7 and 1.0 mm. The range of MIC values was 3.9025–15.625 µg/ml. These results was envisaged the conclusion that derivatives with an aminoindane ring may function as MRSA and *A. baumannii* antibacterial agents.

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1. INTRODUCTION

Aminoindanes are compounds that have a five-membered cyclopentane ring with an amino group and a six-member benzene ring. The pharmacophore features of aminoindane derivatives make them relevant in the realm of medicinal chemistry even though they are often utilized as intermediates in the production of several physiologically active chemicals (Sainsbury *et al*., 2011). The pharmacological effects of aminoindane derivatives include antibacterial (Osowole *et al*., 2012), antiviral (Ugliarolo *et al*., 2012), antiapoptotic (Thiry et al., 2006), antipyretic (Barlow and Walsh, 2008), analgesic (Barlow and Walsh, 2010), anticonvulsant (Chazalette *et al*., 2004), and antiparkinson (Bertolini *et al*., 1992) activity. For example, *5-methoxy-2-aminoindane* **(1)**, *5-methoxy-6-methyl-2-aminoindane* **(2)**, *5,6-methylenedioxy-2-aminoindane* **(3)** and *N-methyl-2-aminoindane* Psychoactive drugs such as aminoindane **(4)** are used commercially (Coppola and Mondola, 2013) (Figure 1).

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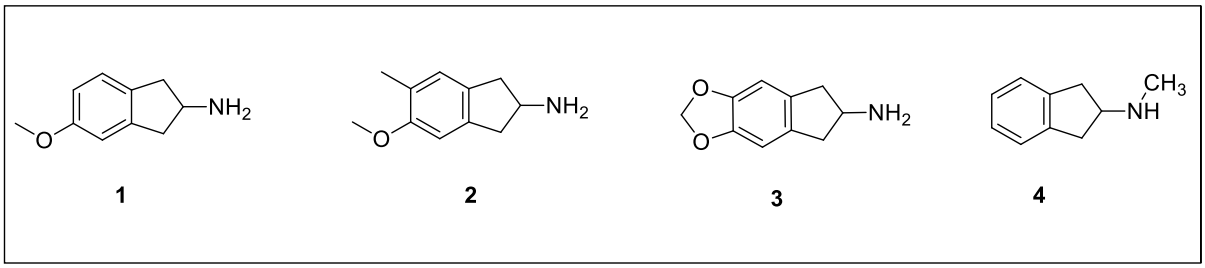
Figure 1. Some aminoindane drugs **1-4**.

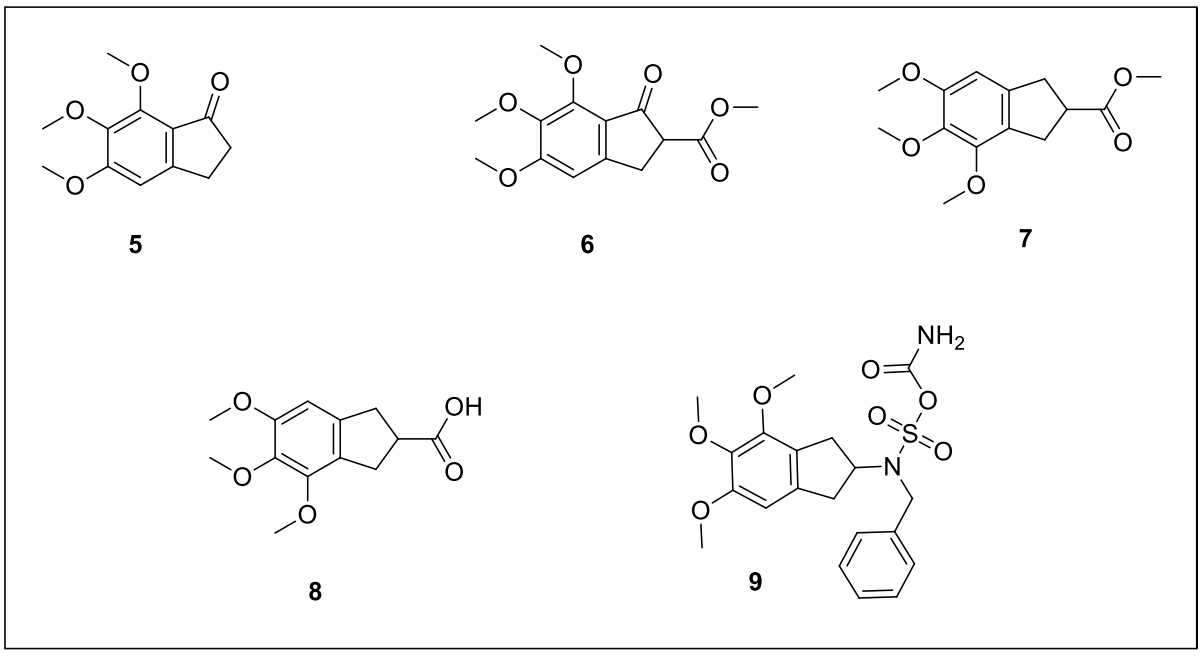


The most often isolated bacterium as a nosocomial infectious agent is *A. baumannii*, which is also antibiotic-resistant. *A. baumannii* is a non-motile, Gram-negative, non-fermenting, catalase-positive, oxidase-negative coccobacillus that is frequently identified in the hospital setting and has gained importance recently (Pompilio *et al*., 2021). Treatment for *A. baumannii* is challenging due to the organism's multidrug resistance (Kyriakidis *et al*., 2021).

S. aureus is a bacterial organism that causes serious infections. Particularly MRSA isolates, which have numerous drug resistances, produce serious infections. The most common cause of sepsis is thought to be a *S. aureus* infection acquired in the community (Turner et al., 2019). Hospital acquired infections are most frequently caused by MRSA isolates. *S. aureus* is resistant to harsh environmental conditions including dryness, high temperatures, and excessive salt because of its sporeless reproduction, but this also raises the risk of infection spread and limits treatment choices (Cheung *et al*., 2021).

This research sought to investigate the antibacterial activity of the previously synthesized (Ozgeris et al., 2015) aminoindane derivatives *5,6,7-Trimethoxy-2,3-dihydro-1H-inden-1-on* **(5)**, *Methyl-5,6,7-trimethoxy-1-oxo-2,3-dihydro-1H-inden-2-carboxylate* **(6)**, *Methyl-4,5,6-trimethoxy-2,3-dihydro-1H-inden-2-carboxylate* **(7)**, *4,5,6-Trimethoxy-2,3-dihydro-1H-inden-2-carboxylic acid* **(8)** and *Benzyl-N-(4,5,6-trimethoxy-2,3-dihydro-1H-inden-2-yl)sulfamoyl carbamate* **(9)** (Figure 2). MRSA and *A. baumannii*, two nosocomial pathogenic pathogens, served as the test group for the compounds antibacterial activity.

Figure 2. Aminoindane derivatives



2. MATERIAL and METHODS

2.1. Chemical and Material

Dimethyl sulfoxide (DMSO) (Merck) was used as a negative control and dissolving compound. For antimicrobial analyzes, Luria Bertaini Agar (LBA) (Difco) Mueller Hinton Agar (MHA) (Oxoid) and Mueller Hinton Broth (MHB) (Biolife), Netilmicin disc (Bioanalyse) were used as positive controls.

2.2. Instrumentation

Thermo Scientific MultiSkan Go model UV-VIS spectrophotometer was used for all spectrophotometric measurements. A quartz cuvette was used in the scan (200 - 400 nm) to determine the wavelength that gives the maximum absorbance. 96-well plates were used for all other measurements.

2.3. Strains of Bacteria

A. baumannii (ATCC BAA-1605) and MRSA (ATCC 43300), pathogenic microorganisms obtained in the culture collection of Erzurum Technical University, were employed for antibacterial activity assays. After a 24-hour incubation at 37°C, microorganisms were cultured in Luria Bertani Agar (LBA) medium and employed in investigations.

2.2.1. Research on Microbes Utilizing Disc Diffusion Analysis

One of the most used techniques for antibacterial testing, the disk diffusion test, uses a bacterial inoculum that has been distributed into MHA medium in accordance with 0.5 McFarland's instructions. Adsorbed substances were prepared as 1000 µg/ml (1 µg active substance + 100 µl DMSO + 900 µl dH_2O) and placed in petri plates in three replications. Microorganisms' antibacterial sensitivity was assessed by measuring the zone diameters that developed after incubation for 24 hours at 37°C. Netilmicin was chosen as the study's preferred positive control since it provided for the evaluation of the activities of the synthesized compounds. 10% DMSO was utilized as a negative control since the synthesized compounds were dissolved in it. The zone diameters of the compounds whose activity was determined as a result of the disk diffusion test were evaluated (Özgeriş *et al*., 2021).

2.2.2. MIC-Based Antimicrobial Research

The Minimum Inhibition Concentration (MIC), also known as the lowest antimicrobial agent concentration that inhibits bacterial growth, was established using the microdilution technique after the activities of the synthesized compounds were assessed in vitro. In the procedure to be used for this, 100 µl of MHB and 100 µl of synthesized compounds were added to each well of the 96-well plates. By using the serial dilution technique, starting with the first well, the compound's concentration was decreased from 1000 µg/ml to 1.95 µg/ml. The lowest concentrations that stop bacteria from growing and don't have any visible turbidity were identified as MIC values after 100 µl of bacterial culture inoculum adjusted according to 0.5 McFarland was added. The turbidity formed in the wells after the 24-hour incubation period was read in the spectrophotometer (600 nm wavelength) (Gormez *et al*., 2015).

3. RESULTS and DISCUSSION

3.1. Antimicrobial Activity

3.1.1. Antibacterial Effect

By using the disk diffusion and microdilution methods, the antibacterial activity of aminoindane derivatives synthesized against *A. baumannii* and MRSA was evaluated. These investigations revealed no zone image that would prevent the bacterial development of **5**, **6**, and

7 compounds. However, it was discovered that compounds **8** and **9** prevented the growth of the MRSA and *A. baumannii* bacteria. Further zone diameters are measured (Table 1).

Table 1. Disc diffusion analysis results of aminoindane derivatives.

Bacteria Strain	(8)	(9)	Control**
A. baumannii ATCC BAA- 1605	0,9*	1,0*	1,2
MRSA ATCC 43300	0,8*	0.7*	1,0

* zone diameter (cm) ** Positive control: netilmicin

The minimal inhibitory concentration of the aminoindane compounds **8** and **9** that have antibacterial activity against MRSA and *A. baumannii* was established. The MIC concentration is detailed in Table 2.

Table 2. Disc diffusion analysis results of aminoindane derivatives.

Bacteria Strain	(8)	(9)
A. baumannii ATCC BAA-1605	3,9025*	3,9025*
MRSA ATCC 43300	15,625*	3,9025*

*The MIC concentration value was calculated as µg/ml.

The antibacterial action of compounds having an aminoindane ring is well reported in the literatüre (Osowole *et al*., 2012). It was found that aminoindane derivatives showed antibacterial activity and that the most effective compound's MIC value was 500 µg/ml in the study by Patel et al. (2010) that investigated at the antibacterial activity of synthetic aminoindane derivatives against Gram-positive and Gram-negative pathogens. Gram negative *A. baumannii* and Gram positive MRSA were shown to be resistant to the antibacterial activity of **8** and **9** aminoindane derivatives in our investigation. Additionally, the fact that the MIC values in the research were lower than those in the literature demonstrates the superior efficacy of the **8** and **9** compounds. However, the investigation reveals that none of the compounds of aminoindane are antimicrobial. Although they are compounds with the same skeleton structure, the source of this condition is assumed to be caused by the varying structures in their side groups. Because compound **9** contains a sulfamoyl carbamate (Güller *et al*., 2021) functional group and compound **8** has carboxylic acid (Yang *et al*., 1997; Ukhov *et al*., 2011) in the variable group. In terms of numerous biological functions, it is well-known in the literature that these functional groups support the skeletal structure (Radadia *et al*., 2005; Dubrovin *et al*., 2015; Jiang *et al*., 2019).

4. CONCLUSION

As a result, the antibacterial activity of derivatives of aminoindane was established. Only **8** and **9** compounds were shown to have low MIC values and activity against *A. baumannii* and MRSA pathogenic microorganisms. These results contribute to the prediction that the compounds **8** and **9** could have therapeutic effects against *A. baumannii* and MRSA infections.

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Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research publishing ethics. The scientific and legal responsibility for manuscripts published in NatProBiotech belongs to the author(s).

Author Contribution Statement

Damla Ruzgar: Studied antimicrobial activity. **Yusuf Akbaba:** Synthesized target products. **Bunyamin Ozgeris:** Synthesized target products and wrote the manuscript. **Arzu Gormez:** Designed the activity studies.

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