REVIEW

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BIOLOGICAL SCREENING AND STRUCTURE-ACTIVITY RELATIONSHIP OF BENZANILIDE

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ABSTRACT:

Benzanilide is an aromatic amide that is of importance as an intermediate in the synthesis of several organic compounds. It is usually prepared by condensing benzoic acid with aniline, catalyzed by acidic or dehydrating agents. The compound has some interesting physicochemical properties; it is crystalline and only moderately soluble in organic solvents. Its use is found in chemical industries involving dyes, pharmaceuticals, and agrochemicals, in which it can be used as a precursor or stabilizing agent. In addition, benzanilide is widely studied in organic chemistry education because of its straightforward synthesis and role in illustrating amide bond formation, which is fundamental to peptide and protein chemistry.

KEYWORDS: Anticancer, Antioxidant, Benzanilide, SAR, Antimicrobial, Anti-inflammatory

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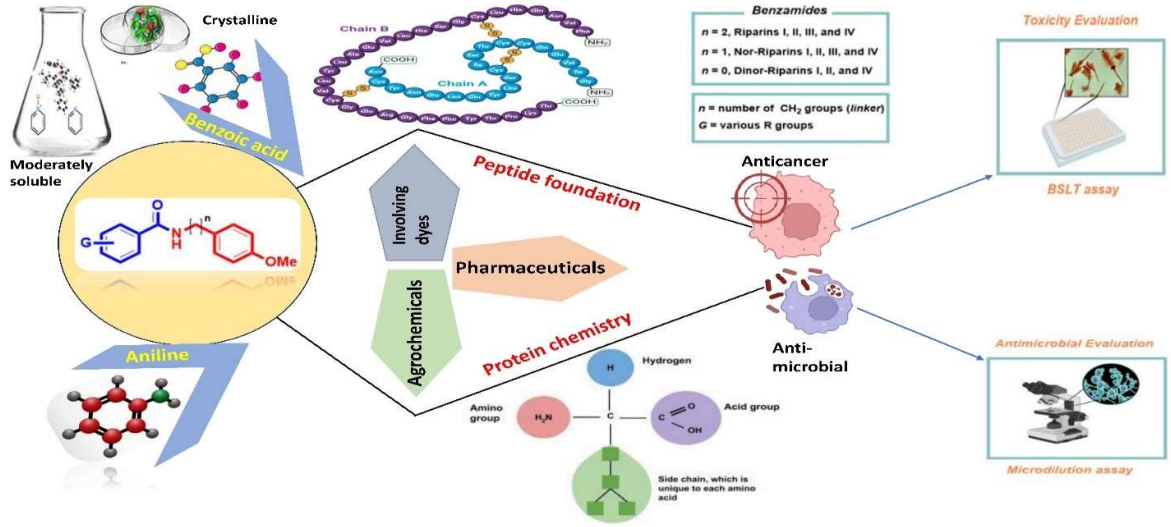
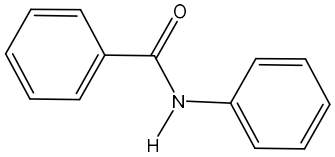
Graphical Abstract:



INTRODUCTION:

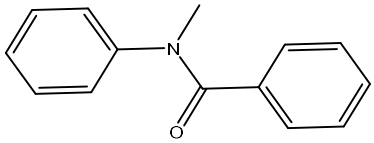
A brief Introduction

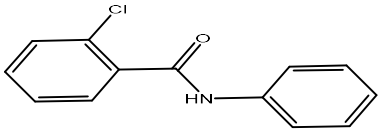
An amino group is attached to benzene ring in the aromatic compound benzanilide (fig 01). It's a heterocyclic compound which has anticancer, anti-inflammatory, antioxidant, analgesic, anti-inflammatory, antibacterial, antiviral, antifungal, antimicrobial, and other properties.



N-Phenylbenzamide

O-Chlorobenzanilide and N-methylbenzanilide are benzanilide derivatives that are widely available. O-Chlorobenzanilide is an antidepressant drug, whereas N-methylbenzanilide is an antimicrobial activity.





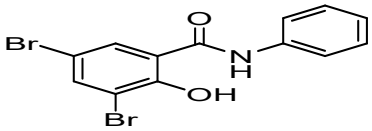
Because of their potential to interact with a wide range of biological targets, benzilides and their derivatives are important in medicinal chemistry (1). The compounds have been found to possess significant antimicrobial, anti-inflammatory, and anticancer activities (2). Because of the ease of chemical modification, medicinal chemists can optimize their pharmacological profiles to enhance their efficacy and safety profiles. This flexibility has made Benzanilide useful in the development of drug research by being the core structure for synthesizing molecules possessing improved biological activities (3).

Benzalnidide-based medications have been pursued for their modulating activity towards specific biological pathways, which would make them an especially valuable aspect in the preparation of highly selective pharmaceutical agents 4. There is, as an example of this, research into the drugs that could constitute cancer therapeutics, where there is promise displayed by Benzanilide-derived compounds in exerting inhibitory effects on growing cancer cells that do not attack healthy tissues much 5. Moreover, their antimicrobial properties make them good candidates for the development of novel antibiotics against resistant bacterial strains (6).

It also has medicinal significance in that its synthesis is through relatively straightforward methods, which has enabled the testing of its derivatives in large amounts. The simplicity in structure of Benzanilide makes it a perfect framework from which chemists can develop new compounds that could be optimized for specific biological activities (7,8).

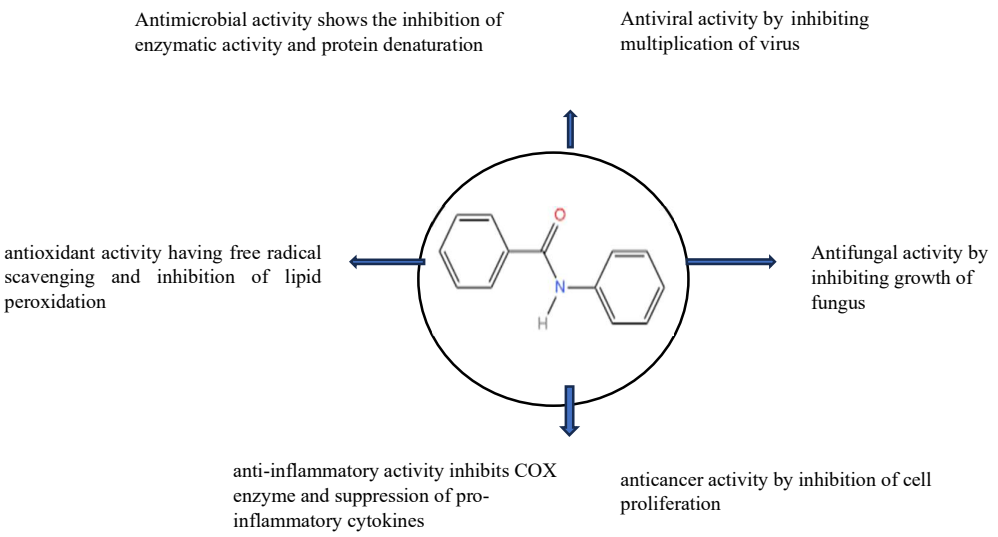
STRUCTURE-ACTIVITY RELATIONSHIP:

The Structure-Activity Relationship (SAR) of Benzalnidide, with a salicylanilide-like structure, is based on the effect of substituents on the salicyl and anilide moieties on its antifungal activity. The 2-hydroxy group on the salicyl ring is important to *Candida albicans* by hydrogen bonding, but acetylation, for example O-acetyl derivatives diminish this activity as they have lost bonding potential. Halogenation at para- or meta-positions (5-monohalo or 3,5-dihalo substitution) greatly improves the activity; specifically, compounds having 3,5-dibromo or 3,5-diiodo substitution were characterized by higher absorption and elimination values. Anionic electron-withdrawing groups (-NO_2) suppress activity while smaller anionic halo substituents (Cl, Br, CF_3) located at the anilide p- or m-position augment both antifungal activity and lipophilicity. Bulky substituents are tolerated if attached at para and improve activity if present on this position. The esterification of the 2-hydroxy group with benzoyl or aroyl derivatives increases the activity against the dermatophytes, such as *Trichophyton mentagrophytes* and *T. asahii*, but the acetyl derivatives lose the activity. For instance, 3,5-dibromosalicylanilide with the formula:



Mechanism of Action of some Benzanilide derivatives:

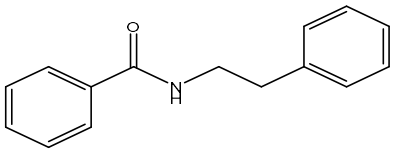
Benzanilide is such a versatile moiety that gives many biological activities that are shown here in the figure below.



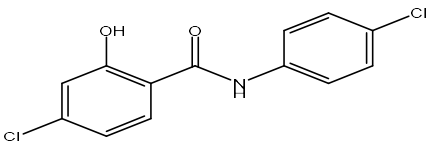
Various biological activities of Benzanilide derivatives

1. Antimicrobial activity: -

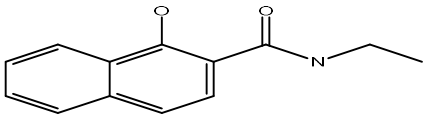
The antimicrobial activity of benzanilide and its derivatives is due to the fact that these compounds may interfere with some essential biological processes in microorganisms by binding to microbial enzymes, proteins, or membranes. Some of the modifications that enhance their activity toward different pathogens include the halogenation and nitro or hydroxyl groups incorporation. They were tested against a broad spectrum of pathogens, including Gram-positive bacteria such as *Staphylococcus aureus,* Gram-negative bacteria such as *Escherichia coli*, and fungi like *Candida albicans*. The use of minimum inhibitory concentration (MIC) and disc diffusion assays further emphasizes the use of these compounds in pharmaceuticals, preservatives, and antimicrobial coatings. The structural diversity of benzanilide derivatives entails the optimization of their antimicrobial efficacy and enlarges their scope of applications (9)



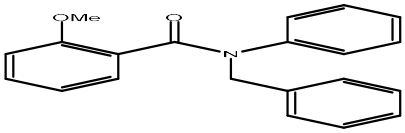
N-(2-phenylethyl)benzamide



4-Hydroxy-N-(4-chlorophenyl)benzamide



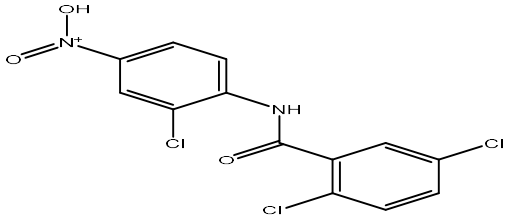
N-Ethyl-1-hydroxy-2-napthamide



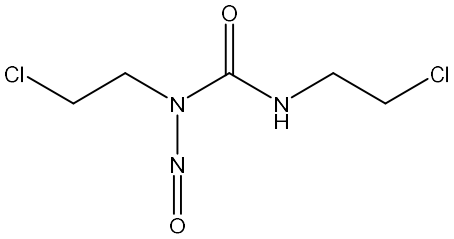
N-benzyl-2-methoxy-*N*-phenylbenzamide

2. Anticancer Activity: -

Benzalanilide and its derivatives were reported to possess anticancer potential primarily due to their interference with critical cellular processes important for tumor growth and proliferation. Modifications in the benzanilide framework through electron-withdrawing or electron-donating groups could enhance the interaction of such molecules with their molecular targets, which could be DNA, enzymes, or receptor proteins important in the process of cancer. The mechanisms through which benzanilides work are the intercalation into DNA, inhibition of topoisomerase, induction of apoptosis, and cell cycle disturbance. These compounds have been shown to be active against several cancer lines, including breast, lung, and colon cancers. Involving cytotoxicity assays such as MTT and determining IC50 will make their development as anticancer drugs possible by structural optimization and targeting specific molecular pathways. (10)



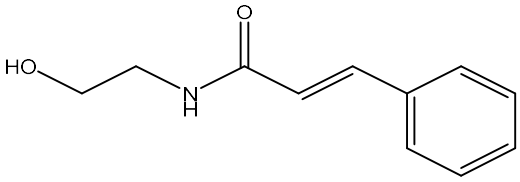
N-(3-chloro-4-(2,5-dichlorobenzamido)phenyl)-N-oxohydroxylammonium



1,3-bis(2-chloroethyl)-1-nitrosourea

3.Anti-inflammatory Effects: -

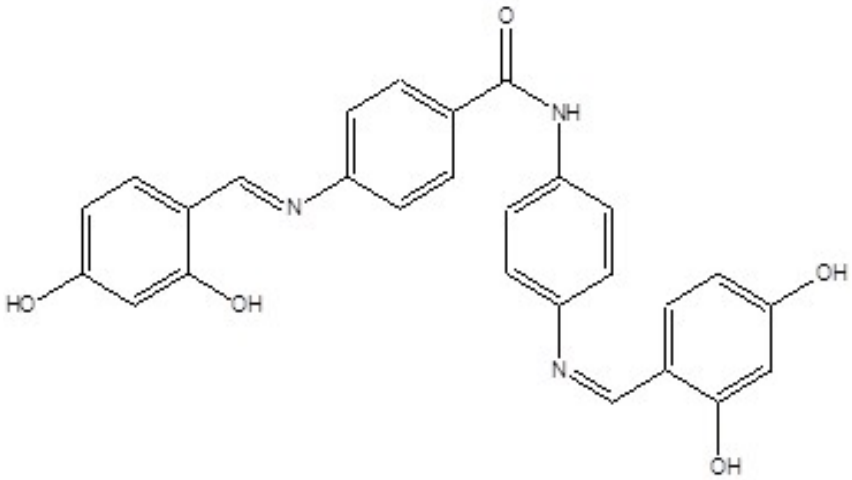
For example, a few aromatic amide compounds, among them benzanilide that is being tested for anti-inflammatory activity, are inspired by the structure-related similarity this compound has toward the structure of NSAIDs. The amide linkage of the benzanilide is postulated to play an important structure that controls its regulation of COX enzymes accountable for the biosynthesis of the pro-inflammatory prostaglandin. The plausibility of aniline and benzoyl to serve as the cause of biological activity has been recognized through the enhanced interaction potentials with inflammatory mediators. Further, benzanilide derivatives showed improved efficacy with reduced toxicity; hence, these are promising candidates for future drug development against anti-inflammatory drugs.(11)



N-(2-hydroxyethyl)cinnamamide

4.Antioxidant Activity

Antioxidant nature of benzanilide as a radical scavenger by DPPH assay is known. In the comparative analysis of amides, benzamidide acts as a radical scavenger of DPPH but less potent than N-(4-hydroxyphenyl)acetamide (acetaminophen). Phenolic –OH group is observed to play an important role for the antioxidant property, thus donating hydrogen and stabilizing the radicals (12).Some other substituted analogs of benzanilide like hydroxyl-substituted derivatives and Schiff bases of benzanilide have also shown antioxidant nature when tested by DPPH assay. Increased potency in hydroxyl-substituted analogs suggests the significance of proper electron-donating substituent in aromatic ring (13).

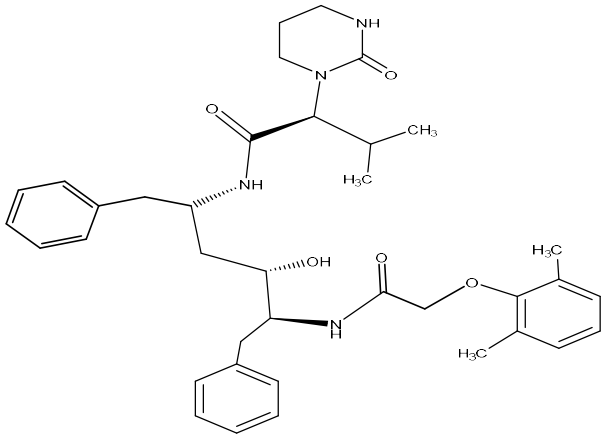


4-(((E)-2,4-Dihydroxybenzylidene)amino)-N-(4-(((Z)-2,4-dihydroxybenzylidene)amino)phenyl)benzamide

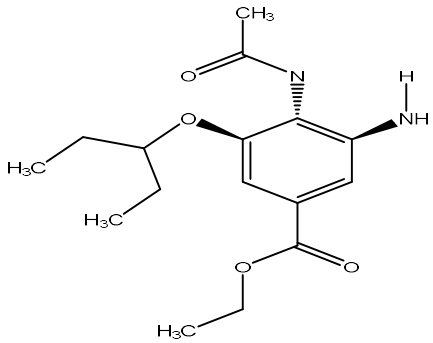
5.Synergistic effects with other drugs: -

Benzanilide is a synthetic compound that has been prepared by the reaction of benzoic acid with aniline. There are studies related to the compound that it might possess pharmacological activities. Anti-inflammatory and analgesic activity was reported; however, details regarding synergistic interaction with other drugs are very limited. In pharmacology, synergism occurs when the effect of two drugs is more significant than the sum of their separate effects. This is especially important in treatments that require higher efficacy, such as in oncology or antimicrobial therapy. For example, some antibiotics can be combined to create a synergistic effect, where the eradication of bacteria is more effective than in monotherapy. For benzanilide, although the derivatives have presented promising anti-inflammatory effects, some of which have been found to be more potent than the reference drugs, like aspirin, there is no study on the interaction of the drug with other drugs. The gap in this knowledge underlines the need for systematic studies in order to evaluate the possibility of synergistic interactions when benzanilide is administered in association with other drugs. (14,15)

Benzanilide has been found to possess promising therapeutic potential when used in combination with a variety of drugs in different fields. In antimicrobial studies, its combination with rifampicin increases the antibacterial activity against *Mycobacterium tuberculosis* , and its synergy with ciprofloxacin increases the efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA). In anticancer research, benzanilide combined with doxorubicin enhances anticancer effects in human breast cancer cells, and its combination with cisplatin increases cytotoxicity against human lung cancer cells. Antiviral combination of benzanilide with oseltamivir significantly enhances the antiviral efficacy against the influenza virus, while combination with lopinavir enhances the antiviral activity against HIV-1. Neuroprotective formulations of benzanilide with memantine show synergistic protection in Alzheimer's disease models, and its combination with riluzole enhances neuroprotection in ALS models (16,17).



(S)-N-((2S,4S,5S)-5-(2-(2,6-dimethylphenoxy) acetamido)-4-hydroxy-1,6-diphenylhexan-2-yl)-3-methyl-2-(2-oxotetrahydropyrimidin-1(2H)-yl) butanamide



Ethyl 4-acetamido-3-amino-5-(pentan-3-yloxy) benzoate

RESEARCH GAP-ANALYSIS:

Though benzanilide derivatives have been known for their various properties such as antimicrobial, anticancer, anti-inflammatory, and antioxidant activities, there is no scientific information regarding any correlations between these properties and the structural and molecular behavior of this class of drugs. Thus, drug interaction, selectivity, toxicity, and effectiveness in vivo are not well studied. Hence, there should be a detailed analysis of these aspects of the drug to explore its pharmacological importance.

CONCLUSION:

Thus, benzamides and their derivatives have always attracted attention of specialists of organic and medicinal chemistry due to possibility of getting various derivatives by structural modifications of their core. Various approaches to the synthesis of benzamides and its derivatives have been described. Traditional approaches, as well as one-pot syntheses, multicomponent reactions and green approaches to the synthesis have been applied for obtaining compounds with better yield, using less number of reagents and producing less amount of wastes.

A great number of biological activities has been demonstrated in the course of various biological tests of benzanilide derivatives. These compounds possess antibacterial, antifungal, anti-inflammatory, antiviral, anticancer and neuroprotective properties. Thus, it is possible to state that benzanilide core might be used as a base for developing biologically active compounds. At the same time, biological responses depend on nature and position of substituents on aromatic rings that is why studying structure-activity relationships should be performed for identifying structural features of a molecule which are responsible for a certain property.

It is necessary to perform additional research to clarify the mechanisms of action of promising derivatives, as well as their selectivity, toxicity, and pharmacokinetic properties. Besides, more thorough in vivo studies are required before considering these compounds for further preclinical development and possible therapeutic application.

Author's Contribution:

The author played a role in the conceptualisation and design of the study, literature search, data collection and analysis, data interpretation, drafting and revising the manuscript, and gave the final approval for the manuscript to be published.

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