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Research

Synthesis and Antimicrobial Evaluation of 1,4 -Naphthoquinone Derivatives as Potential Antibacterial Agents

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Abstract:

1,4-Naphthoquinones are an important class of compounds present in a number of natural products. In this study, a new series of 1,4-naphthoquinone derivatives were synthesized. All the synthesized compounds were tested for in vitro *antimicrobial activity. In this present investigation, two Gram-positive and five Gram-negative bacterial strains and one pathogenic yeast strain were used to determine the antibacterial activity. Naphthoquinones tested for its antibacterial potencies, among seven of them displayed better antimicrobial activity against* Staphylococcus aureus *(*S. aureus*; 30–70 µg/mL). Some of the tested compounds showed moderate to low antimicrobial activity against* Pseudomonas aeruginosa *(*P.aeruginosa*) and* Salmonella bongori *(*S. bongori*; 70–150 µg/mL). In addition, most active compounds against* S. aureus *were evaluated for toxicity to human blood cells using a hemolysis assay. For better understanding, reactive oxygen species (ROS) generation, time-kill kinetic study, and apoptosis, necrosis responses were investigated for three representative compounds.*

Keywords: *1,4-Naphthoquinones, natural product,* Pseudomonas aeruginosa, Salmonella bongori.

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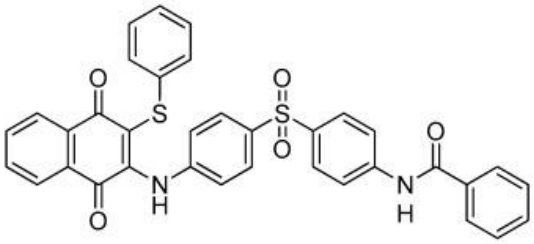
Introduction:

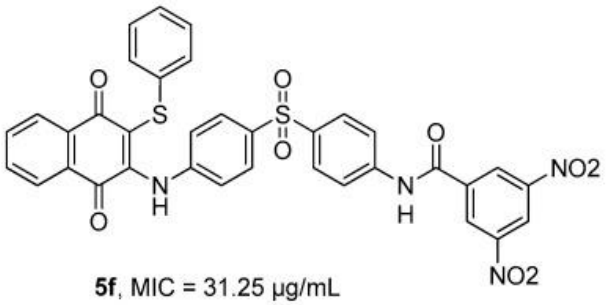
The World Health Organization listed bacterial infections as a foremost threat to global public health. Based on calculations, multidrug-resistant bacterial pathogens are responsible for almost 25,000 deaths in Europe every year.[1,2] The ESKAPE pathogens such as Enterococcus faecium (E. faecium), Staphylococcus aureus (S. aureus), Klebsiella pneumoniae (K. pneumoniae), Acinetobacter baumannii (A. baumannii), Pseudomonas aeruginosa (P. aeruginosa), and Enterobacter spp. are the most common microorganisms causing life-threatening infections. Approximately 40 % of hospital-acquired bacterial infections are induced by these pathogens, and most are resistant to commonly used antibiotics.[3] A joint program for development of effective antimicrobial agents has been initiated by 18 European countries and Canada. Therefore, antibacterial agents capable of fighting infections and spread of antibiotic resistance are currently needed.[4]Regarding the development of effective antimicrobial agents, naphthoquinones have been the focus of extensive research due to their varied functions and clinical applications.[5] A number of natural products contain the naphthoquinone moiety as the core structure. One example is vitamin K, which plays a significant role in bone metabolism, vascular biology, and regulation of blood coagulation in humans.[6] 1,4-Naphthoquinones consist of two ketone groups as vital chromophores that can donate or accept electrons (redox) in a number of biological systems. In recent studies, the inhibitory mechanism of 1,4-naphthoquinone was shown to involve the production of active oxygen species (ROS) by redox cycling, alkylation, or intercalation in the DNA double helix of biomolecules.7,8 1,4-Naphthoquinones and its related compounds are

well-established for irreversible complexation during ROS generation in proteins, which leads to loss of protein function.9 Due to these properties, 1,4-naphthoquinone derivatives exhibit biological properties such as antimicrobial,10 antimalarial,[11] antitubercular,[12] anticancer,[13] and trypanocidal activities.

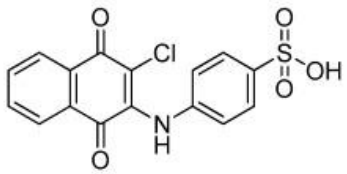
Recently, antimicrobial activities of 1,4-naphthoquinone derivatives have attracted much attention.[15,16] Pingaew et al.[17] reported the synthesis of novel 1,4-naphthoquinone-based sulfonamides and antimicrobial and anticancer potentials (compound I). Cardoso et al.18 performed the synthesis and antibacterial evaluation of sulfonamide-based lapachone derivatives (compound II). Yıldırım et al.19 reported the synthesis of 2,3-disubstituted-aryl-phenylthio-1,4-naphthoquinones as potential antimicrobial agents (compound III). Tandon et al.20,21 described the synthesis and biological evaluation of several new sulfanyl aminonaphthoquinones (compounds IV and V) that displayed important antibacterial activity. Novais et al.22 also reported 1,4-naphthoquinone-based sulfanyl derivatives, and their resistance toward Gram-negative bacteria in biofilms was investigated (compound VI). However, the detailed toxicity and action mechanism for these reported naphthoquinones in humans are unknown to date (Figure 1).



5a, MIC = 15.6 µg/mL



5f, MIC = 31.25 µg/mL



5x, MIC = 31.25 µg/mL

where, MIC = Minimum Inhibition Concentration

1,4-naphthoquinone, a raw ingredient in drugs, agrochemicals, and other beneficial compounds, belongs to the quinine family. It can be released into the environment as a chemical adjuvant in the production of dyes and pharmaceuticals, as well as algicide and fungicide. It is possible that the biodegrade is evenly distributed in the soil, moderately in the surface water, and may be affected by the weather.[14] Vitamin K is a group of 1,4-naphthoquinone compounds that have been shown to help build blood clots. Antibiotics are divided into two categories: antibacterial and antifungal. They are also said to have anti-cancer skills. Vitamin K-based proteins have recently been identified as important for bone and vascular health. Vitamin K, which contains vitamin K1 and vitamin K2, is a group of naturally occurring chemicals. Vitamin K3 (menadione) is often used as a model quinine in cell culture and in vivo studies. It goes with redox cycling processes and arylation, both common to quinones and have biological effects. The ability of menadione to kill cancer cells is linked to the activity of a small family group of MAPK (mitogen-activated protein kinase) called extracellular signal-regulated kinase (ERK 1 and ERK 2). For decades, 1,4-naphthoquinones have been used in cosmetics and home remedies. Henna, for example, is a paste prepared from the powdered leaves of the Lawsonia alba plant, which contains lawone (2-hydroxy-1,4-naphthoquinone), skin and hair dye and pthoquinone), plumbagin (2-methyl-5-hydroxy-1, 4-naphthoquinone), and lapachol [2-hydroxy-3- (3methyl 2-butenyl) -1,4-naphthoquinone]. performing trypanocidal activities against various trypanosomes and Leishmania, causing various human diseases such as African sleeping sickness (Trypanosoma brucei rhodesiense and Trypanosoma brucei gambiense), Kala-azar (Leishmania donovani), and

Chagas disease (Trypanambioma brucei and rhinocerosoma brucei) Trypanosoma cruzi). Only a few biological responses produced by 1,4-naphthoquinone derivatives include antibacterial, antifungal, anti-inflammatory, antithrombotic antiplatelet, antiviral, anticancer, antiallergic, apoptotic, lipoxygenase, scavenging radical, and anti-ringworm. 1,4-naphthoquinone derivatives have been shown to contain human DNA inhibitors topoisomerase I and II.They can also produce active forms of oxygen (ROS) such as semiquinone and hydroxyl radicals by enzymatic reduction (eg. NADPH-cytochrome P 450 reductase).[18]

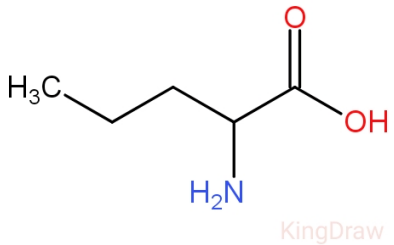
A wide range of plants, fungi, and mammals contain naphthoquinones. Their biological functions have been studied, as well as their effect on prokaryotic and eukaryotic cells. Plumbagone, juglone, and lawone are plant-derived naphthoquinones that have anti-bacterial properties for aerobic and anaerobic bacteria, and Fusarium solani produces naphthazarin toxins (5,8-dihydroxy-1,4 -naphthoquinone) which attacks plants, other fungi, and bacteria. Alkannin and shikonin, along with some of them, are effective against Gram-positive bacteria such as Staphylococcus aureus, Enterococcus faecium, and Bacillus subtilis, but inert anti-Gram-negative bacteria such as Staphylococcus aureus, Enterococcus faecium, and Bacillus subtilis harmful bacteria.2,3-diamino-1,4-naphthoquinone was found to have antibacterial activity against S. aureus, with IC50 values ranging from 30 to 125 lg / mL. A small bactericidal filter of 2,3-diamino-1,4-naphthoquinone was greater than 500 lg / mL, suggesting that its effect was bacteriostatic. Raised in harsh environments, carnivorous plants have developed different ways of catching insects and eating their parts. The production of secondary metabolites containing the amino-naphthoquinone moiety in insect trap tissue also defines food. Chemical, biotic, or immune suppression causes the formation of secondary protective metabolites in many plants. Amino-naphthoquinones are found in several Caryophyllales plants, including Nepenthaceae, Droseraceae, Plumbaginaceae, Drosophyllaceae and Ebenaceae, and are considered promising medicinal properties. In vitro tests revealed that the other 2,3-di substitutes 1,4-naphthoquinones were as effective as the clinically used drugs fluconazole and Amphotericin-B. [19-22]

In addition, 4-aminoquinolines (chloroquine [CQ] for adults / amodiaquine for children) have been used as long-acting first-line antimalarials. However, since the mid-1970s, the therapeutic efficacy of 4-aminoquinolines, especially CQ, has declined. Malaria is a deadly malignant disease that kills two million people every year. Antimalarials are the most common treatment for malaria, but additional antiretroviral drugs that work on all types of parasite are much needed. Several synthetic and natural naphthoquinones have reported aminonaphthoquinones, a class of anti-malarial chemicals that have anti-malarial activity against Plasmodium falciparum, as a potential anti-malarial drug. 2-amino-3-chloro-1,4-naphthoquinone is the most potent of these chemicals. It is much stronger than the W2 clone, with an IC50 of 0.18 lM (37.3 ng mL-1).At IC50 of 0.23 lM, CQ had lower IC50 than others (72 ng mL-1). It has the ability to destroy the D6 clone. Both the 2-amino-1,4-naphthoquinone and the 4-amino-1,2-napthoquinone analogue have shown promising anti-malarial activity in the bioassay. On the other hand, the amount of 2-hydroxy-1,4-naphthoquinones and dimineric quinones were less effective.

AMINO ACID

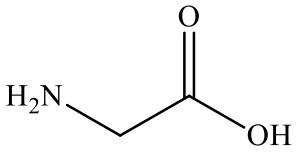
Amino acids are the basic unit of square measure supermolecular. Amino Acids Associate Degree Cluster | Amino | Group | Radical | Chemical group} and group group. Amino acids play a major role in regulating multiple processes associated with the organic phenomenon, as well as modulating the function of proteins that mediate messenger RNA (mRNA) translation. The square measure of amino acids is used to form supermolecular. If the amino acids have a square measurement error, then supermolecular synthesis will not occur. The result can be supermolecular disease. Need a diet that contains all the essential amino acids. Exocrine gland in vivo and in vitro Square measurement of specific amino acids to control the secretion of hypoglycemic agent from the exocrine gland severely and insignificantly. The square measure of amino acids is classified into acidic, primary and neutral amino acids. Some amino acids are not synthesized in the body and are needed in the diet. Essential amino acids are called the square measure of amino acids. The square measure of some amino acids is synthesized in the body and they do not need to be taken in the diet, the square measure of the amino acids are called such unnecessary amino acids. Although the square footage of some amino acids is synthesized in the body, their production is low, the square measure of amino acids being semi-essential amino acids. Amino acids contribute to the formation of tissue supermolecules. Some amino acids are related to the square measure catalyst structure. Hormones such as endocrine square measure created with hypoglycemic agent, somatotrophin and amino acids. Adrenaline, nor-adrenaline and T

square measure created by a single organic compound. Glutathione, a physically active amide, is created with the addition of amino acids. Square measurement of amino acids related to the synthesis of animal pigment. It has been studied that amino-acid balance in cancer patients is generally different in healthy people due to metabolic changes (June et al., 2010). In hepatic cirrhosis of the liver function of nerve fiber cells (DCs), impaired and cirrhotic patients may have reduced plasma branch-chain amino acid levels.[23]



Examples of some important essential Amino Acids

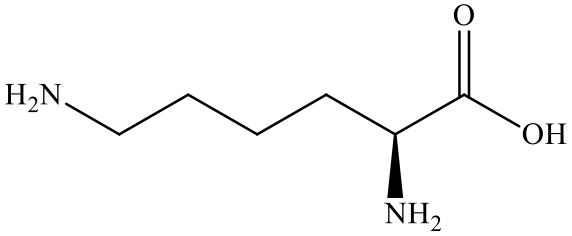
Glycine, the simplest amino acid, obtainable by hydrolysis of proteins. Sweet-tasting, it was among the earliest amino acids to be isolated from gelatin (1820). Especially rich sources include gelatin and silk fibroin. Glycine is one of several so-called nonessential amino acids for mammals; i.e., they can synthesize it from the amino acids serine and threonine and from other sources and do not require dietary sources. It is the only achiral proteinogenic amino acid. It can fit into hydrophilic or hydrophobic environments, due to its minimal side chain of only one hydrogen atom.



glycin

Lysine

Lysine is one of nine essential amino acids in humans required for growth and tissue repair, Lysine is supplied by many foods, especially red meats, fish, and dairy products. Lysine seems to be active against herpes simplex viruses and present in many forms of diet supplements. The mechanism underlying this effect is based on the viral need for amino acid arginine; lysine competes with arginine for absorption and entry into the cell. L-lysine is an L-alpha-amino acid; the L-isomer of lysine. It has a role as a micronutrient, a nutraceutical, an anticonvulsant, an Escherichia coli metabolite, a Sccharomyces cerevisiae metabolite, a plant metabolite, a human metabolite, an algal metabolite and a mouse metabolite. It is an aspartate family amino acid, a proteinogenic amino acid, a lysine and L-alpha-amino acid.It is a conjugate base of a L-lysinium. It is a conjugate acid of a L-lysinate.



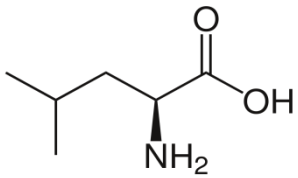
lysin

L-lysine

Leucine

Leucine is one of nine essential amino acids in humans (provided by food), Leucine is important for protein synthesis and many metabolic function. Leucine contributes to regulation of blood-sugar level; growth and repair of muscle and bone tissue; growth hormone production; and wound healing. Leucine also prevents breakdown of

muscle proteins after trauma or severe stress and may be beneficial for individual with phenylketonuria. L-leucine is the L-enantiomer of leucine. It has a role as a plant metabolite, an Escherichia coli metabolite, a Saccharomycescerevisiae metabolite, a human metabolite, an algal metabolite and a mouse metabolite. It is a pyruvate family amino acid, a proteinogenic amino acid, a leucine and a L-alpha-amino acid. It is a conjugate base of L-leucinium. It is a conjugate acid of an L-lucinate.



L-Leucine

Conclusion

In all, quinones have been added as a new and appealing template for leishmanicidal LdGSK-3s inhibitors, active on two quite different Leishmania species, from a clinical perspective. These naphthoquinones showed a multi target leishmanicidal mechanism that may also encompass the respiratory chain, as it is the case here. Far from being detrimental for its pharmacological development, this fact presents an immediate advantage to curtail resistance induction by target mutation. As such, multi target drugs have been hailed as relevant approach for neglected tropical diseases with miltefosine as a paradigm, in tune with a current trend that advocate for a polypharmacology approach for neglected diseases.

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