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REVIEW ON SYNTHESIS AND EVALUATION OF NOVAL BENZOFURAN DERIVATIVES AS POTENT IMMUNOMODULATORY ANTIBACTERIAL ACTIVITY

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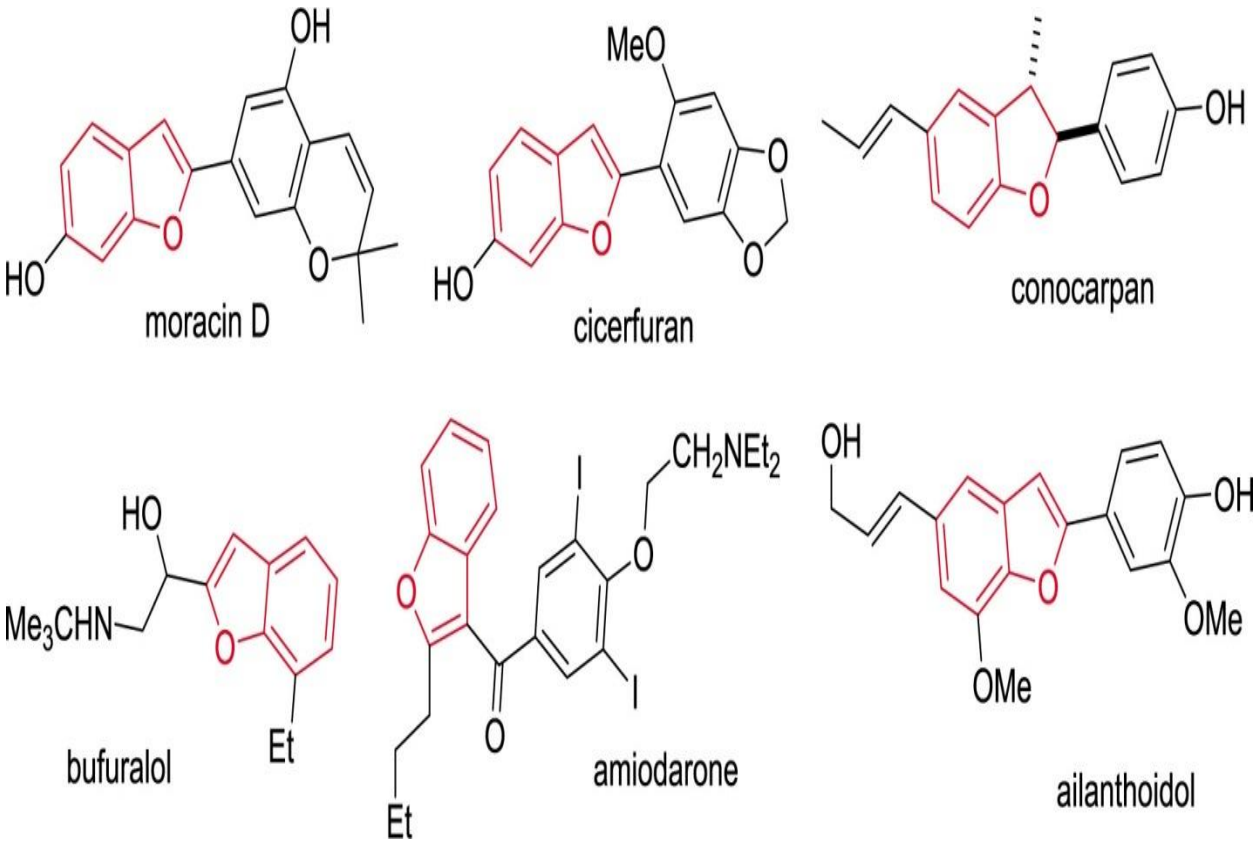
Abstract:
Benzofuran derivatives have attracted significant attention in recent years due to their diverse pharmacological activities, including antibacterial and immunomodulatory properties. This review aims to provide a comprehensive overview of the current knowledge regarding the antibacterial activity and immunomodulatory effects of benzofuran derivatives. The potential mechanisms of action and structure-activity relationships of these compounds will also be discussed. Understanding the therapeutic potential of benzofuran derivatives in combating bacterial infections and modulating immune responses can pave the way for the development of novel and more effective antibacterial agents and immunomodulators.
Keywords: Benzofuran, antibacterial activity, immunomodulation, structure-activity relationships, bacterial infections, immune-related disorders.

Introduction:
Bacterial infections continue to pose a significant global health challenge, and the emergence of antibiotic-resistant strains has further complicated treatment options. In addition, immune dysregulation and inflammatory disorders are also prevalent in various pathological conditions. Therefore, the search for novel antibacterial agents and immunomodulators is of utmost importance. Benzofuran, with its unique structural characteristics, has shown promising potential in combating bacterial infections and modulating immune responses. Bacterial infections remain a major global health concern, and the emergence of antibiotic-resistant strains has further exacerbated the problem. Consequently, there is an urgent need for the discovery and development of new antibacterial agents with novel mechanisms of action. Additionally, modulation of the immune system plays a crucial role in various disease states, including autoimmune disorders and cancer. Benzofuran derivatives have emerged as a promising class of compounds with potential antibacterial and immunomodulatory activities.[1]



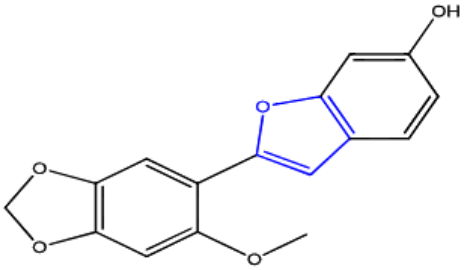
Numerous studies have been conducted to prepare specific target structures from natural sources or using synthetic methods as a result of the wide range of biochemical activities of different benzofurans. The stem bark, root bark, and leaves of different mulberry trees were used to extract a number of arylbenzofurans, some of which were also produced via multistep syntheses [4,5]. The synthesis of benzofurans can be accomplished in a number of ways, including the metal-free cyclization of ortho-hydroxystilbenes via hypervalent iodine reagents [6], the isomerization of suitable precursors [7,8], the cross-coupling of silanols with aromatic halides via alkali-metal salts [9,10], the addition of potassium aryltrifluoroborates to aliphatic nit

The development of AMR and the choice of highly virulent bacterial strains were significantly influenced by the widespread use of various antimicrobials in the veterinary and agricultural sectors [4–7]. The DR pathogens with veterinary origins can spread to humans and further colonise the environment [8,9]. Additionally, via horizontal gene transfer, the genetic elements that code for AMR phenotypes can spread further and accumulate in different bacterial species [10,11]. Bacterial resistance to two or more antimicrobial drugs was the result of this vicious cycle, which produced multidrug-resistant (MDR) pathogens that harboured multiple resistance mechanisms [12]. The development of novel drugs that specifically target MDR pathogens is crucial to solving this issue.

The most common cause of hospital-acquired infections worldwide is the ESKAPE group of pathogens, which includes enteric bacteria faecium, the bacteria Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas and the Enterobacter species complex [13–15]. These both types of bacteria can cause infections that are fatal in people who are critically ill, have a compromised immune system, or both [15]. In addition to placing a heavy burden on healthcare systems, the rising antimicrobial

resistance among ESKAPE pathogens has significant global economic costs. Thus, it is crucial to create novel drugs that specifically target the clinically significant multidrug-resistant ESKAPE group of pathogens. Because of the wide range of biological activity and well-known chemical properties of p-aminobenzoic acid (pABA) and its derivatives, there is a great deal of pharmacological and commercial interest in these compounds. pABA is widely present in nature and is highly abundant in a variety of plant and animal species.[16]

Several approved medicines are obtained from natural sources and demonstrate a wide spectrum of pharmacological activity [11,12]. Benzo furan, a naturally occurring heterocyclic that is often encountered, plays a significant role in both drug development and chemical biology. Cicer bijugum, a wild species of chickpea, has the first naturally occurring hydroxylated benzofuran cicerfuran(I), which has been detected in the roots and is thought to play a significant role in the plant's defence mechanism against Fusarium wilt.



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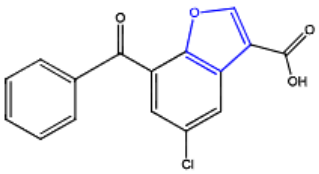

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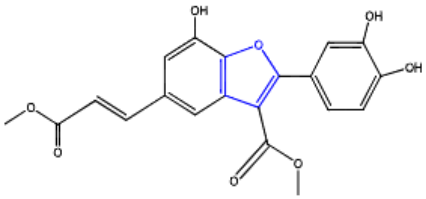

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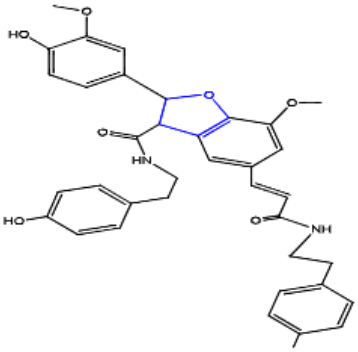


IV

As analgesics (e.g., BRL 37959, II) and prospective anti-cancer medicines, these benzofruans are broadly rooted in synthetic and physiologically intriguing molecules (III and IV). In addition to being utilised in a variety of chemical and agricultural disciplines, In addition to being used as anti-oxidants and brighteners, substituted benzofuran is also used to treat ulcers, rheumatism, and ulcerative colitis. [13]

Antibacterial Activity of Benzofuran:

Numerous studies have demonstrated the antibacterial activity of benzofuran and its derivatives against a wide range of bacterial pathogens. The mechanism of action varies among different compounds, including inhibition of DNA gyrase, interference with cell membrane integrity, disruption of bacterial biofilms, and inhibition of essential bacterial enzymes. These findings suggest that benzofuran compounds hold promise as effective antibacterial agents, both alone and in combination with existing antibiotics. [17-19], antibacterial activity of benzofuran derivatives. Numerous studies have shown that benzofuran compounds have inhibitory effects on a variety of bacterial strains, including both Gram-

positive and Gram-negative bacteria.. The mechanisms of action underlying their antibacterial activity, such as disruption of bacterial membranes, inhibition of essential enzymes, and interference with bacterial cell wall synthesis, will be discussed. Moreover, structure-activity relationships and strategies for enhancing the antibacterial efficacy of benzofuran derivatives will be explored.[20-22]

Immunomodulatory Effects of Benzofuran:

Derivatives of benzofuran have also demonstrated positive immunomodulatory effects. This section emphasises how these substances can modify the immune system by affecting immune cell activity, cytokine production, and immune signalling pathways. The impact of benzofuran derivatives on autoimmune diseases, allergic reactions, and cancer immunotherapy will be discussed. Furthermore, the underlying mechanisms responsible for their immunomodulatory effects, including regulation of inflammatory mediators and modulation of immune cell function, will be elucidated.benzofuran has also shown immunomodulatory effects. It controls the activation and proliferation of immune cells, such as macrophages, T cells, and B cells, as well as the production of pro-inflammatory cytokines like interleukins (ILs) and tumour necrosis factor-alpha (TNF-alpha). Moreover, benzofuran derivatives have demonstrated anti-inflammatory properties by inhibiting various signaling pathways involved in immune responses. These immunomodulatory effects make benzofuran an intriguing candidate for the treatment of immune-related disorders.[23-25]

Synthesis of benzofuran:

The earliest type of benzofuran produced using coumarin was coumarone. As per Figure 3,4, the middle 3,4-dibromo-3,4-dihydro coumarin goes through a PERKIN reworking with KOH to create benzofuran.

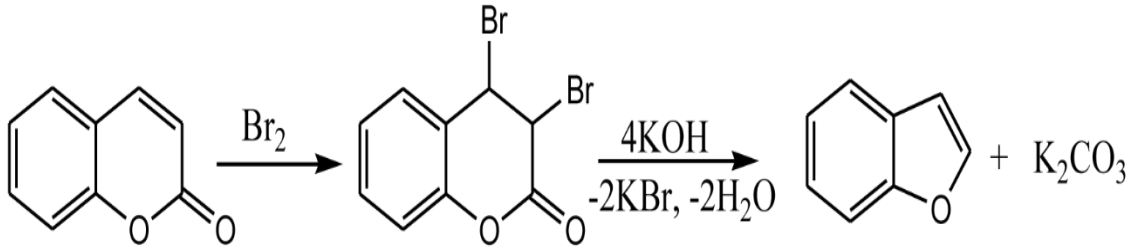


Figure 3: 2- Alkylbenzofurans are created by the warm cyclodehydration of 2-alkylphenols.

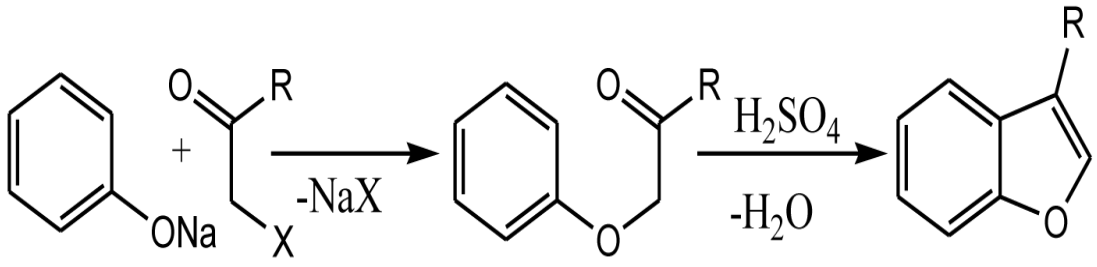
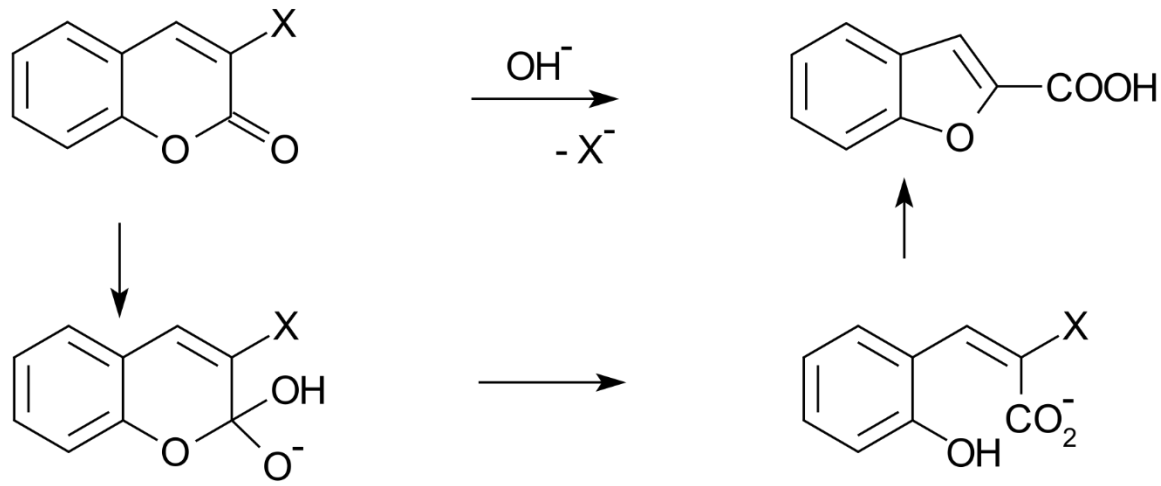


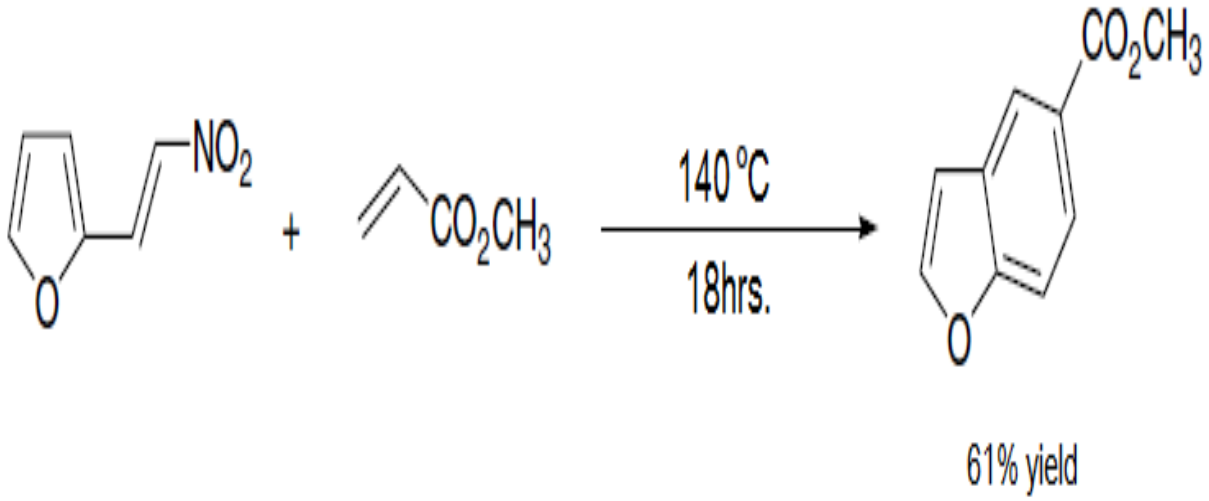
Figure 4: Halo ketones and phenolates blend to produce benzofurans, which are then dried out utilizing zeolites, polyphosphoric corrosive, or H2SO4 [26-27]

The examination has shown an extensive variety of creation strategies for benzofurans. Investigate these examples:

1) When coumarin and hydroxide consolidate, it is known as the Perkin response. [28].

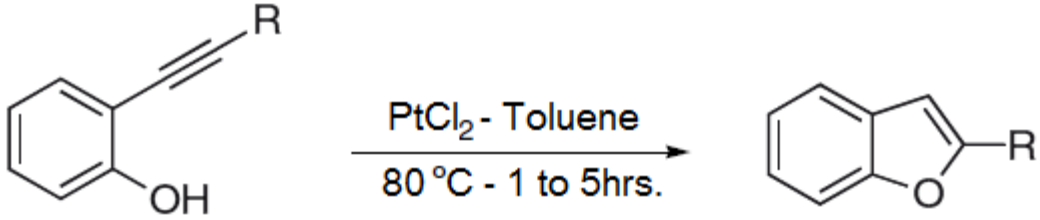


2) Nitro vinyl furans go through the Diels-Birch response with a scope of dienophiles. [28]:



61% yield

3) Utilizing an alkyne ortho substituent to cycle a phenol [43]:



> 88% yield

The bicyclic ring benzofuran, generally known as coumarone, is made when the five-membered furan ring and the benzene ring join.[28]

Antimicrobial activity of Benzofuran-

The antibacterial movement of the test materials was thought about involving the agar cup plate strategy in contrast to the microbes Bacillus subtilis, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa.[37] In the agar material that was sullied with the microorganisms, cups with a 10 mm measurement were made utilizing a sterile drill. Utilizing the spread plate strategy, 0.1 mL of inoculums were scattered all through the agar plate. The cups were loaded up with unequivocally estimated (0.1 mL) arrangements of each made prescription and benchmark tests. The plates were all saved in a cooler at 2-8 °C for two hours to permit the test synthetic substances and principles to diffuse well. There were plainly particular zones of restraint by and large around the cup, showing the antibacterial impact. To survey the adequacy of the dimethyl sulphoxide (DMSO), which filled in as a removing dissolvable, the dissolvable control was done simultaneously. The zone of restraint's breadth was estimated and recorded.[29-30]

Structure-Activity Relationships:

The structure-activity relationships (SAR) of benzofuran derivatives play a crucial role in determining their antibacterial activity and immunomodulatory effects. This section explores the key structural features required for optimal activity, such as substitutions on the benzene ring, the presence of heteroatom's, and modifications of the furan moiety. Understanding SAR can aid in design and development for more potent benzofuran-dependent antibacterial compounds and immunomodulators. Understanding the structure-activity relationships of benzofuran derivatives is crucial for the design and synthesis of more potent and selective compounds. This provides an in-depth analysis of the structural features of benzofuran derivatives that contribute to their antibacterial and immunomodulatory activities. It also explores various strategies employed to optimize their pharmacological properties, such as structural modifications, formulation approaches, and combination therapies.[30]

Challenges and Future Perspectives: Despite the promising findings, there are several challenges and limitations associated with the use of benzofuran compounds. These include potential toxicity, bioavailability issues, and the need for further in vivo studies. Overcoming these challenges will be vital for translating benzofuran-based compounds into clinical applications. Future research directions and strategies for optimizing benzofuran compounds as antibacterial agents and immunomodulators are discussed.[31-33]

METHODOLOGY

In both homogeneous and heterogeneous catalytic pathways, several techniques have been devised for the synthesis of benzofuran. The only reactions covered here, though, are those that are heterogeneously catalysed. Cross-coupling reaction of sonogashira b/w o-halo phenol and terminal alkynes processed by sequential 5-endo - dig cyclization is one of the finest ways to obtain benzofuran derivatives.[32-35]

Mattio, L.M et al Benzofuran-containing molecules called dehydro—viniferin (1, Figure 1) was discovered to be effective against Gram-positive bacteria. Foodborne pathogen Listeria monocytogenes Scott A, employed as a model for Gram-positive bacteria, was demonstrated to be particularly susceptible to its antimicrobial action (MIC and MBC values of 4.42 and 35.3 M, respectively) [35-36]. Due to depolarization of membrane, morphological alterations & loss of membrane integrity, the substance seriously damages the cytoplasmic membrane.

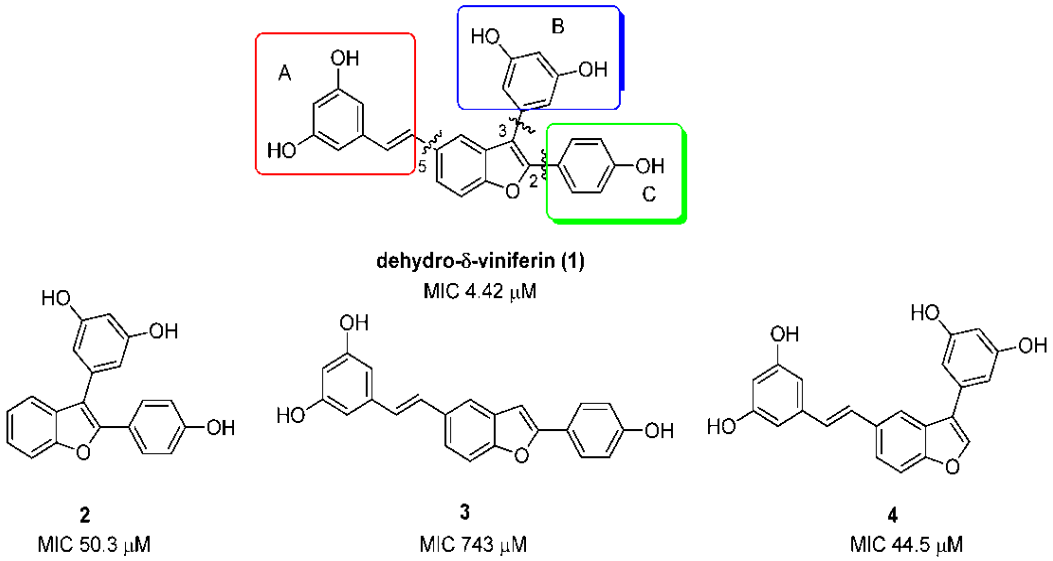


Figure5-Model compounds 2, 3, and 4's structures and MIC values

Conclusion:

Benzofuran and its derivatives possess significant antibacterial activity and immunomodulatory effects. The diverse mechanisms of action and the ability to modulate immune responses make benzofuran an intriguing scaffold for the development of new antibacterial agents and immunomodulators. Further research is warranted to fully understand the structure-activity relationships and optimize the pharmacological properties of benzofuran compounds for therapeutic applications. This review concludes by summarizing the current understanding of the antibacterial activity and immunomodulatory effects of benzofuran derivatives. The potential of these compounds as promising agents in the treatment of bacterial infections and immune-related diseases is highlighted. Moreover, future research directions and challenges in this field are discussed, emphasizing the need for further investigations to fully exploit the therapeutic potential of benzofuran derivatives.

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CONFLICT OF INTEREST

None

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