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SYNTHESIS OF NOVEL CHALCONE DERIVATIVES BEARING 2,4-THIAZOLIDINEDIONE AS POTENTIAL ANTIBACTERIAL AGENTS

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ABSTRACT

Back ground: The emergence of antibiotic-resistant bacteria presents a significant challenge to public health, necessitating the development of novel antibacterial agents. The synthesis was achieved through a series of reactions, including Claisen-Schmidt condensation followed by cyclization, yielding a range of chalcone-thiazolidinedione hybrids.

Objective: To synthesize some novel chalcone derivatives bearing 2,4-thiazolidinedione and evaluate the antibacterial activity.

Method: New 2,4-thiazolidinedione derivatives were synthesized by Knoevenagel condensation and aryl/alkyl halide's reaction. Products were purified by TLC and screened for antibacterial activity against various pathogens using MIC determination. For antibacterial activity, the optical density (OD600) of cultures was measured and diluted to ~10^6 CFU/ml. Controls included cells and media alone, and Ceftriaxone was used as a reference. MIC values were recorded after 16-18 h of incubation at 37°C.

Results: The chalcone derivatives with 2,4-thiazolidinedione (7a-d) are screened for antibacterial activity against Gram-positive and Gram-negative bacteria. Some compounds showed activity against Gram-positive bacteria, particularly multidrug-resistant strains, with compound 7a being the most potent. The chalcone and thiazolidine rings were crucial for activity, indicating potential for further development.

Conclusion: Notably, the presence of the 2,4-thiazolidinedione moiety was found to significantly enhance the antibacterial properties of the chalcone framework. The results suggest that these chalcone-thiazolidinedione derivatives exert their antibacterial effects through disruption of bacterial cell wall synthesis and inhibition of critical bacterial enzymes. Overall, the findings of this study highlight the potential of chalcone derivatives bearing 2,4-thiazolidinedione as a new class of antibacterial agents.

Key words: Chalcone, 2,4-thiazolidinedione, antibacterial activity, Knoevenagel condensation

INTRODUCTION

A chalcone is a simple chemical scaffold of many naturally occurring compounds and has a widespread distribution in vegetables, fruits, teas, and other plants. Since most natural chalcones are brown in color, the word "chalcone" comes from the Greek word "chalcos," which means "bronze". 1,3-diaryl-2 propen-1-one, or chalconoid, is the common chemical framework shared by chalcone molecules. It exists as trans and cis isomers, with the trans isomer being more thermodynamically stable. The phenyl ring attached to the carbonyl group is defined to be the A ring and the other benzene ring is named as the B ring **(Figure 1) [1-3]**.

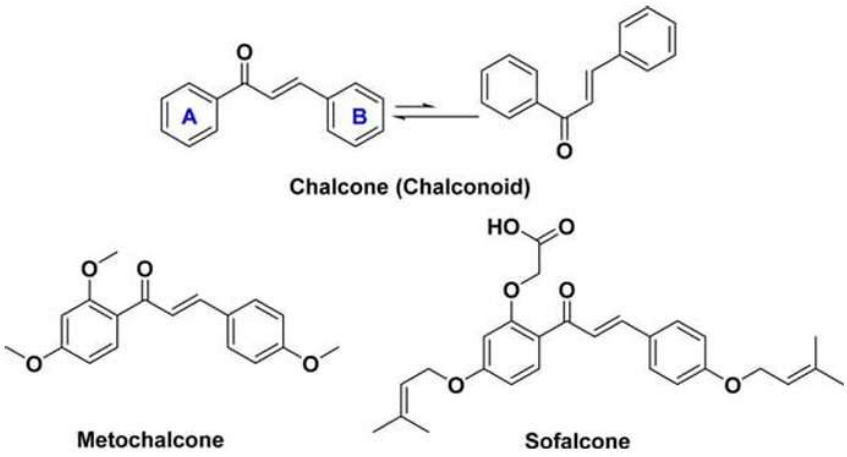

Figure 1: Structure of chalcones

The chalcone family has drawn significant attention due to its wide range of intriguing biological functions, in addition to its synthetic and biosynthetic applications. Chalcones have been used medicinally for thousands of years. During that time, several medical conditions like diabetes, cancer, and inflammation were treated with plants and herbs. For therapeutic application, a number of drugs based on chalcones have received approval. For instance, sofalcone acts as an antiulcer and muco- protective medication, whilst metochalcone was once sold as a choleretic **(Figure 1)**. Chalcones have been

the subject of in-depth research and numerous published minireviews. Nevertheless, little is known about the specific mechanisms of action causing the many biological actions of chalcones. Focusing recent advances in the application of chalcone as a preferred scaffold in medicinal chemistry, this review primarily examines studies that have been published within the last ten years, with a few exceptions. This section will provide an overview of a number of chalcone use elements, such as biosynthesis, synthetic approaches and uses, biological activities and target analysis **[4-7]**.

Degradation techniques catalyzed by bases or acids are commonly used to generate chalcones. Chalcones are a readily generated type of α,β-unsaturated ketone; however, an increasing amount of novel methods and processes have been reported recently because of their fascinating biological activity and the creation of various catalysts or reaction conditions **[8, 9]**. The general protocols, conditions, catalysts, and synthetic methods used in the synthesis of chalcone scaffolds are outlined here.

The aim of the present research work is to synthesis and evaluation of novel chalcone derivatives incorporating a 2,4-thiazolidinedione moiety, and designed to enhance antibacterial efficacy.

MATERIALS AND METHODS

Chemicals and reagents

The chemicals and reagents used in the work were of AR and LR grade, procured from Sisco, SD Fine Chemicals, Spectro Chemicals, Hi-media, Merck.

Methodology [10-14]

The synthesis of novel 2,4-thiazolidinedione derivatives was prepared by 3 steps. Ther are:

Step 1: In this step thiourea (1) is allowed to react with chloroacetic (2) acid in presence of conc. HCl and distilled water for 12 h to form 2,4-thiazolidine-dione (3).

Step 2: Second step involves, the reaction of biphenyl aldehyde (4) with 2,4-thiazolidine-dione in presence of sodium acetate and acetic acid at 100°C for 12 h to form (Z)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzaldehyde (5). This step is also known as "Knoevenagel Condensation".

Step 3: In this final step aryl and alkyl halide (6) reacts with the biphenyl benzaldehyde in presence of potassium carbonate and DMF at 100°C for 2-12 h to form final new derivative bearing 2,4-thiazolidine-dione is (Z)-5-(4-((E)-3-oxo-3-phenylprop-1-en-1-yl) benzylidene) thiazolidine-2,4-dione (7 a-d). Filtered the filtrate and collected the product and tested for isolation by TLC. Total 3 steps are presented in one scheme (Scheme 1).

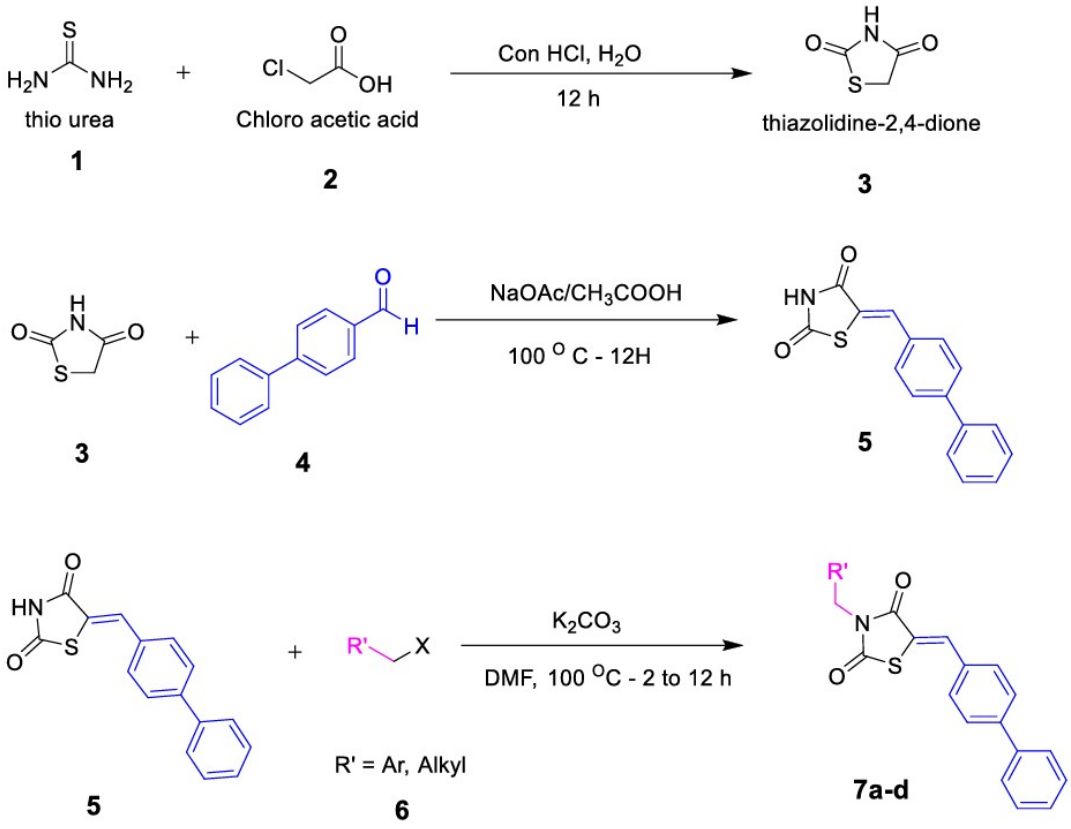

Figure 2: Synthetic scheme for the synthesis of compounds 7a-d

TLC procedure

- TLC is useful for separation or isolation of components from the reaction products. In this experiment TLC was done to know whether the components are isolated or not.
- Take aluminium TLC plate (stationary phase) and mark 4 points with equal distance. Add starting material 1 (biphenyl benzaldehyde) at first point and starting material 2-(aryl or alkyl halide) at second point. Add final product at third point and add filtrate at point 4.
- Place the TLC plate in mobile phase (petroleum ether) and allow the compound to run towards solvent front. Observe the zones under UV spectrophotometer and in iodine chamber.

Screening of antibacterial activity [15-19]

Materials:

The pathogens panel consisted of *Staphylococcus aureus* (ATCC 25923), *Salmonella typhi* (ATCC-14028), *Klebsiella*

pneumoniae (ATCC-33495), *Candida albicans* (ATCC-66027) are MRSA strains were taken. These strains were procured from BEI/NARSA/ATCC (Biodefense and Emerging Infections Research Resources Repository/Network on Antimicrobial Resistance in *Staphylococcus aureus*/American Type Culture Collection, USA) and routinely cultivated on Nutrient Agar (Ref-63971) purchased from SRL Chem. Prior to the experiment, a single colony was picked from plate, inoculated in Nutrient Agar supplemented broth and incubated overnight at 37°C with shaking for 18-24 h to get the starter culture.

Procedure:

Bacterial colonies were cultivated in nutrient agar. The culture optical density (OD600) was determined, and then they were diluted to contain about 106 CFU/ml. This inoculum was introduced into a series of test wells in a microlitre plate containing the substance under test at different concentrations, ranging from 75 to 25 µg/mL. Controls include cells and media alone (without chemical and cells), as well as the ceftriaxone reference standard utilized in the study. The antifungal strain in the experiment was standardized with fluconazole, and plates were cultured at 37°C for 16 to 18 h before the MIC values were recorded based on the presence or lack of discernible growth. MIC values were made separately three times for each compound, each time with triplicate samples.

RESULTS AND DISCUSSION

The synthesis of chalcone derivatives is presented in Scheme 1. Thiazolidine-2,4-dione (3) was prepared by a previously described method in step-1. (Z)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzaldehyde 5 was prepared via Knoevenagel condensation between 3 and biphenyl aldehyde 4 step 2. C-N bond formation between 5 and various aryl and alkyl halides (6a-d) in step-3 afforded the corresponding (Z)-5-(4-((E)-3-oxo-3-phenylprop-1-en-1-yl) benzylidene) thiazolidine-2,4-dione derivatives (7a d). New chalcone derivative was synthesized and sent for structure elucidation through NMR spectroscopy and the structure will be represented as below.

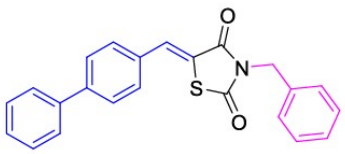

Figure 3: Novel chalcone derivative: (Z)-5-([1,1'-biphenyl]-4-yl-methylene)-3-benzylthiazolidine-2,4-dione

Below graphical representation shows the detailed information about the new chalcone derivative bearing 2,4-thiazolidine-dione [(Z)-5-([1,1'-biphenyl]-4-yl-methylene)-3-benzylthiazolidine-2,4-dione].

Spectra: ^{1}H NMR (300 MHz, CDCl3) δ 7.94 (s, 1H), 7.71 (d, J = 8.3 Hz, 2H), 7.60 (dd, J = 15.0, 7.7 Hz, 4H), 7.53 – 7.30 (m, 8H), 4.92 (s, 2H).

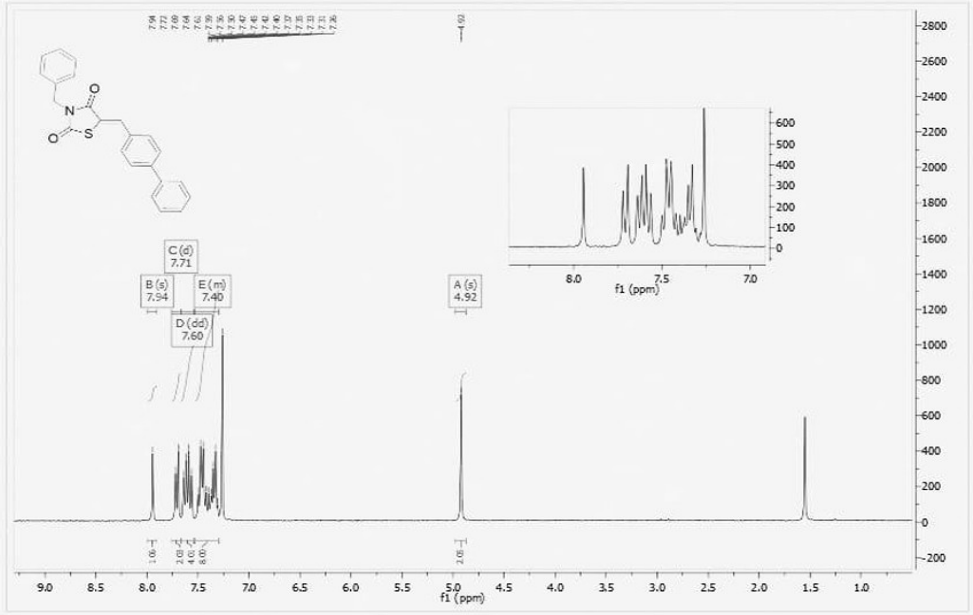

Figure 4: NMR spectrum of novel chalcone derivative

IR Spectrum:

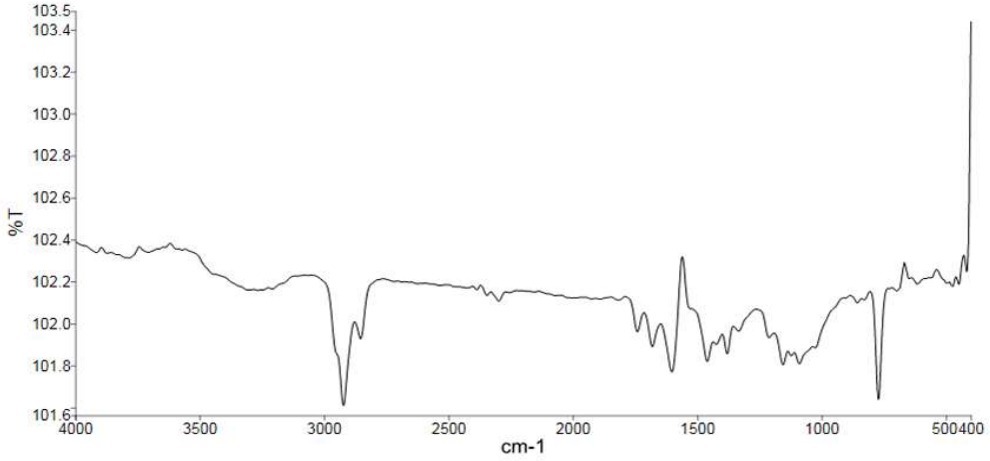

Figure 5: IR spectrum of novel chalcone derivative

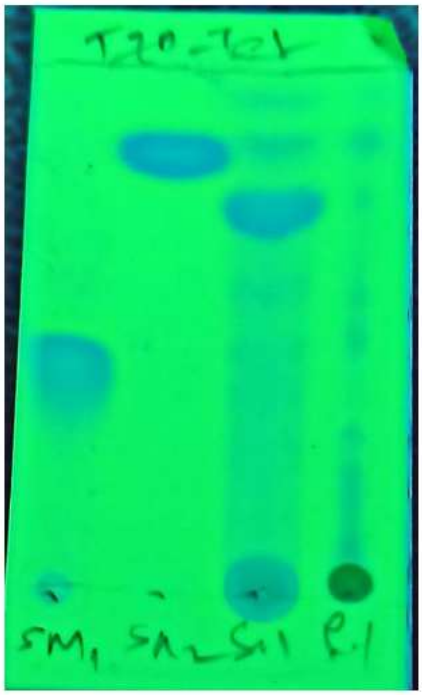

Figure 6: TLC plate under UV spectrophotometer

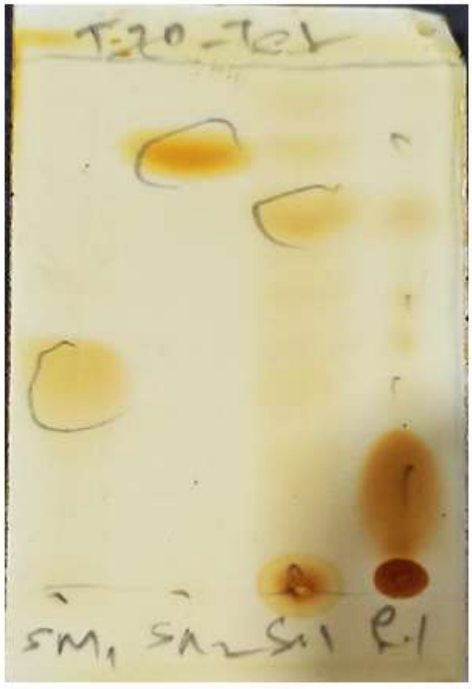

Figure 7: TLC plate in iodine chamber

Newly synthesized chalcones now studied for their antibacterial activity against ESKAP pathogen panel. Minimum Inhibitory Concentration (MIC) was determined by performing antibiotic susceptibility testing on the newly synthesized compounds in

accordance with the standard CLSI guidelines. The concentration of the newly synthesized compounds used is in the range of 75-25µg/mL Ceftriaxone was used as a reference compounds. The results are given in **Table 1**. where only 7a and 7b exhibited moderate activity (supplementary data).

A preliminary *in vitro* assay showed that the intermediate esters 7f did not exhibited any antibacterial activity at 75 mg/ml. Among the desired compounds, 7a, 7b, and 7c showed potent antibacterial activity against Gram-positive strains (*Staphylococcus aureus* ATCC-25923) and their MIC values were in the range of 75-25µg/mL, which was comparable to the control drugs **(Table 1)**.

Table 1: MIC values (µg/mL) of the tested compounds against panel of bacteria and fungi

S.No	*Compound*	*S. aureus* ATCC 25923	Salmonella Typhi ATCC-14028	*K. pneumoniae* ATCC-33495	*candida albicans* ATCC-66027
1	**7a**	25	-	75	75
2	**7b**	50	-	-	-
3	**7c**	50	-	-	-
4	**7d**	75	-	-	-
5	**7E**	-	-	-	50
6	Ceftriaxone	50	50	50	50
7	fluconazole	-	-	-	25

Compound: 7a

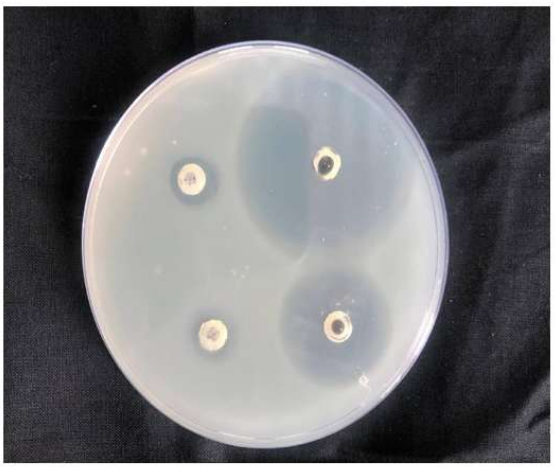

Figure 8: Bacterial strain- *S. aureus*, ATCC-25923

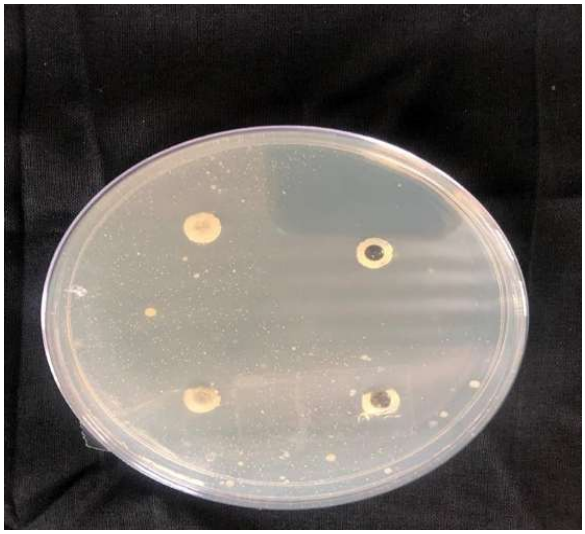

Figure 9: Bacterial strain- *K. pneumoniae* ATCC-33495

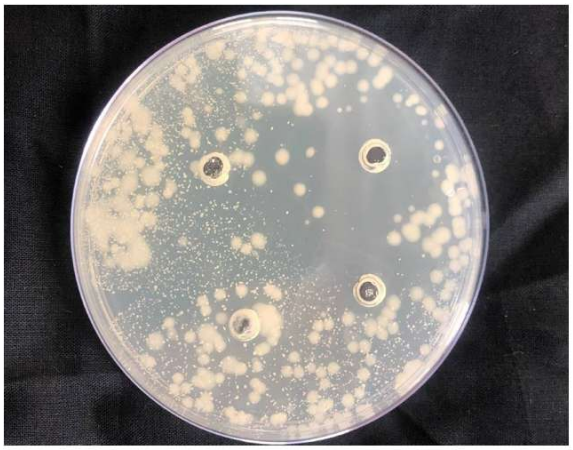

Figure 10: Fungal strain- *Candida albicans*, ATCC-66027

Compound 7b:

Figure 11: Bacterial strain- *S. aureus*, ATCC-25923

Compound: 7d

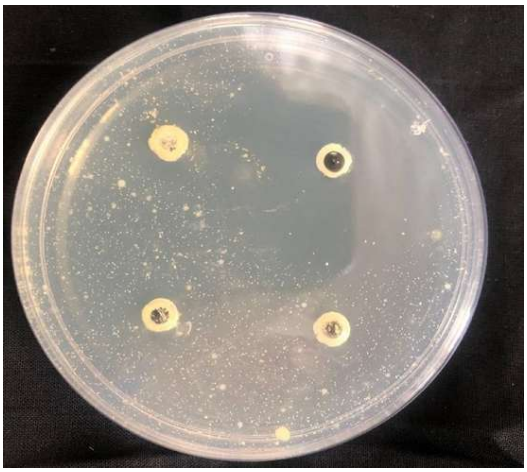

Figure 12: Bacterial strain: *S. aureus*, ATCC-25923

Compound: 7e

Figure 13: Fungal strain: *Candida albicans*, ATCC-66027

CONCLUSION

Synthesized a new series of chalcone derivatives bearing 2,4-thiazolidinedione and their analogues (7a-d) and evaluated for their anti-bacterial activities against Gram- positive and Gram-negative bacteria. Some of the compounds showed antibacterial activities against Gram-positive bacteria, particularly against multidrug-resistant strains of clinical isolates. Compound 7a was found to have the most potent inhibitory capacity. Furthermore, the results suggested that the chalcone and thiazolidine ring seemed to be necessary for the activity and further development of such compounds may be of interest.

Conflicts of interest

None declared.

Ethical approval

Not required.

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