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RESEARCH ARTICLE

MJM BIOLABS

Computational and Experimental Identification of Low-Toxicity Antifungal Compounds for Cryptococcal Meningitis and Candidiasis

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ABSTRACT

Cryptococcal meningitis and candidiasis are life-threatening fungal infections predominantly affecting immunocompromised populations, such as those living with HIV/AIDS. Current antifungal treatments are limited by high toxicity, increasing resistance and accessibility challenges in low-resource settings. This study aimed to identify novel, low-toxicity antifungal compounds using computational drug discovery tools and validate their antifungal potential in vitro. Fluconazole and flucytosine analogues were screened using SwissSimilarity, ZINC Pharmer, SwissADME, and ProTox 3.0 to assess structural similarity, pharmacokinetics, and toxicity. The most promising compounds ZINC79355076 and ZINC000035660397 were evaluated using molecular docking and in vitro agar dilution methods against *Cryptococcus neoformans* and *Candida albicans*. ZINC79355076 demonstrated a superior docking score (-9.7), favorable pharmacokinetics, and lower predicted toxicity compared to fluconazole (-7.5). Similarly, ZINC000035660397 exhibited enhanced binding affinity (-8.1) and a higher LD50 compared to flucytosine. In-vitro assays confirmed that both analogues inhibited fungal growth comparably or more effectively than current standard treatments. ZINC79355076 and ZINC000035660397 analogs are promising drugs for the treatment of cryptococcal meningitis and candidiasis with improved pharmacological profiles and reduced toxicity. Additional in vivo experimentation and clinical trials are recommended to elucidate their therapeutic potential, particularly in resource-limited settings.

Keywords: Cryptococcal meningitis, Candidiasis, Antifungal agents, Drug discovery, Computational screening, Low toxicity

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INTRODUCTION

Fungal infections are becoming a global health problem, particularly among immunocompromised hosts such as HIV/AIDS and cancer patients. *Cryptococcus neoformans* and *Candida albicans* are two of the most significant fungal pathogens with clinical relevance, which produce cryptococcal meningitis and systemic candidiasis, respectively. *Cryptococcus neoformans* is the major cause of cryptococcal meningitis, which is an CNS infection that has fatal prognosis. The organism is typically acquired by inhaling environmental spores, most commonly from soil or bird droppings. Primary respiratory infections are generally asymptomatic but will disseminate to the CNS in individuals with impaired immune defenses and induce meningitis (Liu et al., 2012; Maziarz et al., 2016). Similarly, Candida albicans is an opportunistic commensal pathogen that becomes pathogenic when mucosal barrier is disturbed or the immune system is suppressed. It causes mucosal infection and life-threatening systemic candidiasis in diabetic patients, cancer patients, or long-term corticosteroid-treated individuals (Kullberg et al., 2015; Lopes et al., 2022).

Although antifungal drugs like fluconazole, flucytosine, and amphotericin B exist, their use is limited by toxicity level, failure of CNS penetration, cost, and emerging antifungal resistance (Perfect et al., 2014; Sousa et al., 2023). Amphotericin B is extremely effective but is nephrotoxic and requires strict monitoring. Flucytosine is bone-marrow-suppressing, and fluconazole is hepatotoxic and promotes resistance. Computer-aided drug discovery offers a cost-effective and time-saving method of identifying novel drug leads. Ligand-based screening, molecular docking, and pharmacokinetic modeling are some of the strategies that enable prediction of bioactivity, toxicity, and blood-brain barrier permeability before experimental verification (Brogi et al., 2020; Hassan et al., 2016; Macalino et al., 2015).

This study aimed to identify novel, low-toxicity analogues of fluconazole and flucytosine using a combination of computational and in vitro methods. Two promising compounds, ZINC79355076 and ZINC000035660397, were discovered and evaluated for antifungal activity against *C. neoformans* and *C. albicans*. This integrated approach addresses the limitations of existing therapies and supports the development of safer, more accessible antifungal agents for vulnerable populations, especially in low-resource settings.

METHODOLOGY

Computational Screening and Analysis

Ligand-Based Virtual Screening

The chemical structures of standard antifungal agents – fluconazole, flucytosine, were obtained in SMILES format from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). These reference compounds were used as inputs for ligand-based virtual screening performed on SwissSimilarity (v2020) (http://www.swisssimilarity.ch/), where both two-dimensional (2D) and three-dimensional (3D) similarity searches were conducted against the commercial compound library to identify structurally related drug-like candidates. Additional potential analogues were retrieved through pharmacophore-based screening on ZINCPharmer (v1.3) (http://zincpharmer.csb.pitt.edu/pharmer.html), using the ZINC12 database (https://zinc12.docking.org/).

Pharmacokinetic and Drug-Likeness Prediction

Drug-likeness and pharmacokinetic properties of the identified analogues were evaluated using SwissADME (v1.0) (http://www.swissadme.ch/). Parameters analyzed included compliance with Lipinski's Rule of Five and Veber's criteria, gastrointestinal (GI) absorption, aqueous solubility, blood-brain barrier (BBB) permeability, and predicted interactions with cytochrome P450 (CYP) isoenzymes.

Toxicity Prediction

Toxicological properties were further assessed with ProTox 3.0 (v3.0) (https://tox.charite.de/), which provided predictions of LD50 values, toxicity class assignment, hepatotoxicity potential, and associated toxicity pathways. Analogues with higher predicted LD50 values and minimal organ-specific toxicity were prioritized for molecular docking.

Target-Based Docking

Candidate ligands and reference antifungal agents were prepared for docking by conversion into three-dimensional conformers using Avogadro (v1.2), followed by structural optimization with the MMFF94 force field. Energy minimization and file conversion to MOL2 format were performed using UCSF Chimera (v1.18). Protein targets were obtained from the Protein Data Bank (PDB): lanosterol 14-α-demethylase, the target of fluconazole (PDB ID: 6MA7; UniProt ID: P10613), and cytosine deaminase, the target of flucytosine (PDB ID: 4R88; UniProt ID: A0A0E1CHI1). Preprocessing of protein structures was carried out in Chimera by removing heteroatoms and non-standard residues.

Docking simulations were performed using the AutoDock Vina plugin (v1.1.2) integrated into Chimera. Binding affinities were recorded, and the top-scoring ligand–receptor interactions were visualized and profiled with BIOVIA Discovery Studio Visualizer 2024.

In Vitro Antifungal Assay

Experimental validation of computational predictions was conducted using *Cryptococcus neoformans* and *Candida albicans* clinical isolates. Two lead analogues, ZINC79355076 and ZINC000035660397 (200 mg each), were tested alongside fluconazole (Cosmos Pharma; 800 mg and 1200 mg tablets) as the reference control. Sabouraud Dextrose Agar (SDA) medium was prepared by dissolving 9.75 g of powder in 150 mL of distilled water, autoclaving at 121 °C for 15 minutes, and dispensing into sterile Petri dishes to solidify. Stock solutions of the analogues were prepared by dissolving 200 mg of each compound in 1 mL of dimethyl sulfoxide (DMSO), yielding concentrations of 200 mg/mL, and incorporated into molten SDA before solidification. Fluconazole was prepared by dissolving the tablets in 5 mL of distilled water to obtain concentrations of 160 mg/mL (800 mg tablet) and 240 mg/mL (1200 mg tablet). Control groups included positive controls (fluconazole-incorporated plates) and negative controls (SDA without drug incorporation).

Plates were divided into two halves, with *C. neoformans* inoculated on one side and *C. albicans* on the other. Standardized fungal suspensions of 10^4 CFU/mL were applied to the agar surface using sterile cotton swabs in a zigzag pattern. The inoculated plates were incubated at 35 °C for 24 hours. Antifungal efficacy was evaluated visually by comparing fungal colony density on experimental plates against positive and negative controls, with inhibition defined as complete or significant reduction in fungal growth relative to the untreated control.

Ethical Considerations

This study did not involve human participants or animal subjects. However, all microbial cultures were handled under biosafety level 2 (BSL-2) protocols approved by the research ethics committee of Kabarak University. Approval Reference: KABU01/KUREC/001/10/08/24. The study was conducted between February 2024 and February 2025.

Availability of Data and Materials

Upon request, the corresponding author will make the datasets created and/or examined during the current work available.

RESULTS

In-Silico Screening Results

ZINC79355076 showed a stronger binding affinity and higher LD50 compared to fluconazole. The analogue also demonstrated favorable drug-likeness and BBB permeability.

Table 1:

Comparative Docking and Pharmacokinetic Properties of Fluconazole and its Analogue

Compound	Docking Score	Predicted LD50 (mg/kg)	Lipinski Compliance	Veber Compliance	BBB Permeability	CYP Interactions
ZINC79355076	*-9.7*	1600	Yes	Yes	Yes	CYP2C19, CYP2D6, CYP3A4
Fluconazole	*-7.5*	1271	Yes	Yes	Yes	CYP2C19

The flucytosine analogue, ZINC000035660397, demonstrated improved docking performance and lower predicted toxicity. It complied with pharmacokinetic rules and had minimal interaction with CYP enzymes.

Table 2:

Comparative Docking and Toxicity Profiles of Flucytosine and its Analogue

Compound	Docking Score	Predicted LD50 (mg/kg)	Lipinski Compliance	Veber Compliance	BBB Permeability	CYP Interactions
ZINC000035660397	*-8.1*	2000	Yes	Yes	Yes	Minimal
Flucytosine	*-5.8*	685	Yes	Yes	Yes	Minimal

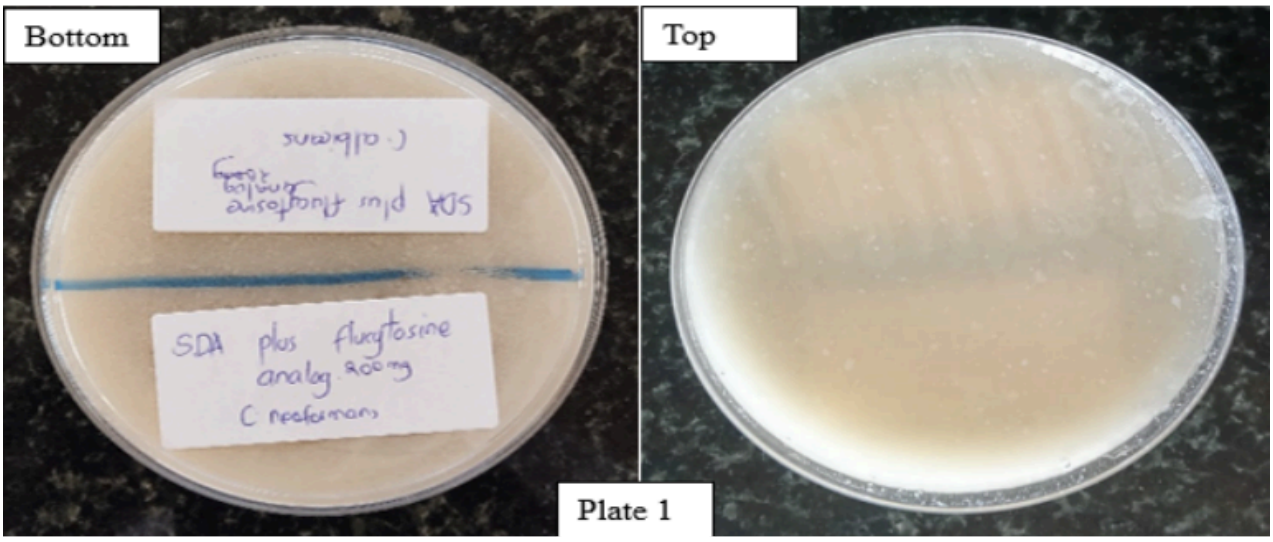
In-Vitro Antifungal Activity

The antifungal activity of ZINC79355076 and ZINC000035660397 was evaluated using the agar dilution method.

ZINC000035660397: Also demonstrated full inhibition of *C. neoformans* and substantial inhibition of *C. albicans*, though slightly less dense compared to ZINC79355076.

Figure 1:

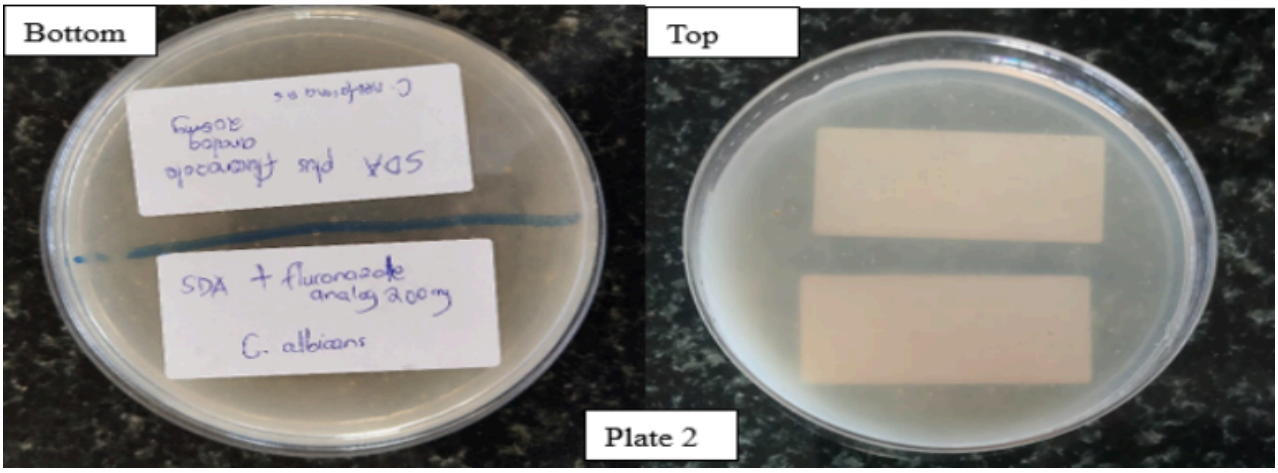
Growth inhibition by ZINC000035660397 on C. albicans (top half) and C. neoformans (bottom half) after 24-hour incubation at 35 °C.



ZINC79355076: Complete growth inhibition was observed against both *C. neoformans* and *C. albicans*, comparable to the positive control fluconazole at 240 mg/ml and 160 mg/ml concentrations.

Figure 2:

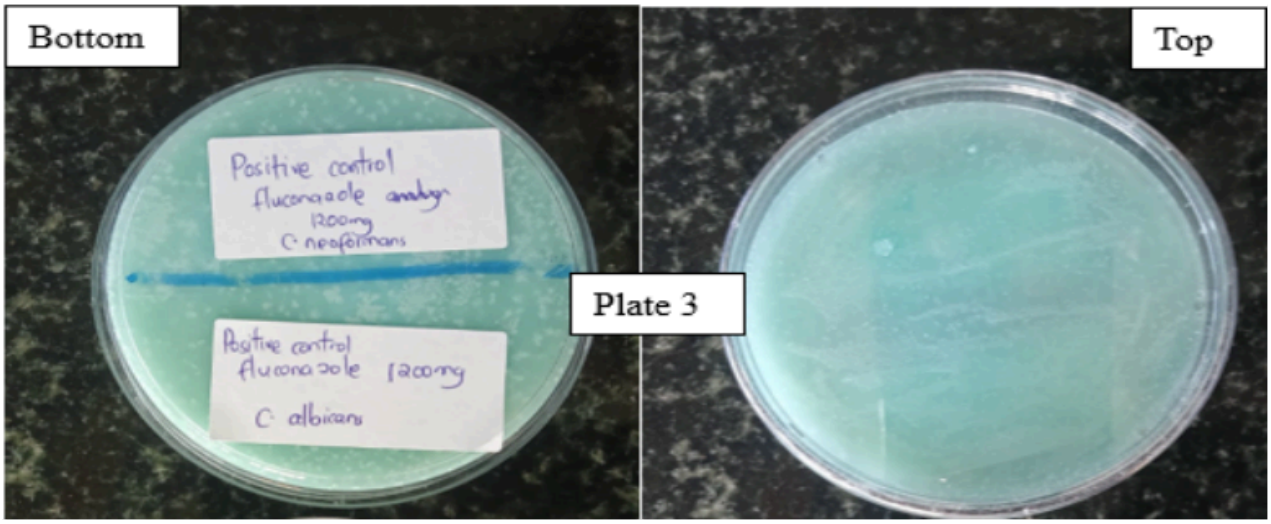
Growth inhibition by ZINC79355076 on C. neoformans (top half) and C. albicans (bottom half) after 24-hour incubation at 35 °C.



Positive Controls: Fluconazole plates (160 mg/mL and 240 mg/mL) showed complete inhibition of both fungal species, confirming experimental reliability.

Figure 3:

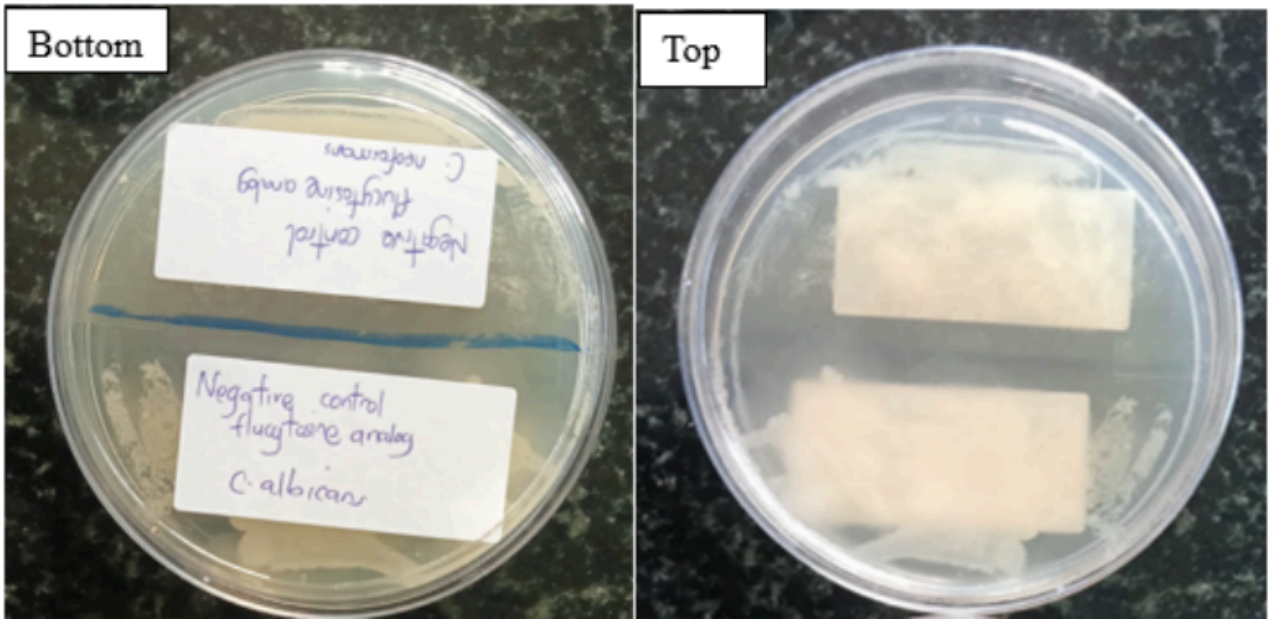
Positive control plate (Fluconazole, 240 mg/mL): No visible growth of C. neoformans (top half) and C. albicans (bottom half) after 24 hours.



Negative Controls: Unmedicated SDA plates demonstrated unrestricted growth of both fungi, validating the viability of fungal strains and the effectiveness of active compounds.

Figure 4:

Negative control plate: Extensive fungal growth for both C. neoformans (top) and C. albicans (bottom).



DISCUSSION

This study identified and validated two promising antifungal compounds, ZINC79355076 and ZINC000035660397, through a combination of computational screening and in vitro evaluation. The compounds demonstrated superior docking performance, improved pharmacokinetic profiles and significantly lower predicted toxicity compared to fluconazole and flucytosine, respectively. The analogue of fluconazole, ZINC79355076, also possessed a high docking score of -9.7 kcal/mol, which is much greater than that of fluconazole -7.5 kcal/mol. All its pharmacological advantages like BBB permeability, adherence to Lipinski's and Veber's rule, and minimal interaction with the CYP enzymes qualify it as a suitable drug for CNS fungal infection like cryptococcal meningitis (Chandrika et al., 2024). This is in line with the fact that structure-based modifications of azole core scaffolds have been shown to enhance antifungal activity and decrease toxicity (Singh et al., 2023). Additionally, ZINC000035660397

exhibited an improved docking score (-8.1 kcal/mol) over flucytosine (-5.8 kcal/mol) and a high predicted LD50 value of 2000 mg/kg indicating lower acute toxicity. The analogue was low in CYP450 interaction and possessed good drug-likeness parameters for systemic delivery. These results are consistent with the current priorities in drug development on pyrimidine analogues with reduced cytotoxicity but increased selectivity (Nahar et al., 2024).

In vitro results reinforced computational predictions. Both analogues inhibited fungal growth effectively, showing comparable performance to fluconazole at 160 mg/mL and 240 mg/mL. Notably, ZINC79355076 achieved full suppression of *C. albicans* and *C. neoformans*, while ZINC000035660397 showed slightly diminished inhibition of *C. albicans*, potentially due to the phenomenon of antifungal tolerance where subpopulations temporarily survive at drug levels above the MIC. The agar dilution method employed in this study was cost-effective and provided visually distinct endpoints for fungal inhibition. Compared to broth microdilution techniques, which are more resource-intensive, agar dilution remains reliable for susceptibility testing particularly in low-resource settings (Poeta et al., 1994; Therese et al., 2006).

The antifungal mechanisms of the analogues align with their respective parent drugs. ZINC79355076 likely targets lanosterol 14-α-demethylase, disrupting ergosterol biosynthesis and compromising fungal membrane integrity. ZINC000035660397 likely inhibits cytosine deaminase, impairing nucleotide metabolism. Ligand-receptor analysis confirmed stable hydrogen bonding with critical active site residues such as ARG A:372 and PHE A:213 for ZINC79355076, enhancing receptor specificity and potency (Ylilauri, 2014). Importantly, both compounds exhibited favorable pharmacokinetic features including high GI absorption and BBB penetration key requirements for treating systemic fungal infections and CNS-targeted conditions like cryptococcal meningitis (Kamakia et al., 2023). The reduced interaction with CYP enzymes also lowers the potential for drug-drug interactions, which is critical in polypharmacy contexts such as HIV/AIDS co-infections (Khan et al., 2024).

The challenge of antifungal resistance is well documented with mechanisms including efflux pump overexpression and target enzyme mutations (Melhem et al., 2024). ZINC79355076, with its proof of superior binding in spite of potential target alterations, can even overcome resistance caused by lanosterol demethylase mutations. Likewise, ZINC000035660397's high LD50 with low CYP interaction decreases the risk of increased pharmacological resistance (Arendrup et al., 2017; Wiederhold, 2017).

Despite such optimistic results, this research is far from without limitation. The experiment involved only two fungal strains, and activity against a wider spectrum needs to be determined. Besides that, in vivo pharmacokinetics, toxicity, and therapeutic activity need to be determined. Further research has to be done to perform MIC determination, cytotoxicity against human cell lines, and in vivo using appropriate animal models (Dolan et al., 2009; Rivera et al., 2023). Their potency, low toxicity, and drug-likeness position the analogues favorably as drugs of choice for combination therapy. Evidence from literature establishes that combinations of antifungals are more potent and can delay resistance onset especially in resource-limited settings (O'Hanlon Cohrt et al., 2018).

Conclusion

This study gives compelling evidence for the antifungal activity of ZINC79355076 and ZINC000035660397, fluconazole and flucytosine analogues respectively. They had superior docking scores, better pharmacokinetic profile, lower predicted toxicity, and effective in vitro inhibition against *Cryptococcus neoformans* and *Candida albicans*. These findings point towards their potential as second-generation antifungal drugs, particularly in the management of CNS and systemic mycoses in resource-limited settings. Follow-up studies must include in vivo validation, cytotoxicity assays against human cells, and testing of generalized antifungal spectrum for their therapeutic use.

Conflicts of Interest

All authors declare no conflict of interest.

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Authors' contributions

KR: Conceptualization, methodology, in silico analysis, in-vitro experiments, data analysis, writing original draft, draft review, Project administration. **SLA**: In silico analysis, methodology, in vitro experiments, writing – original draft, draft review. **SKO**: In silico analysis, methodology, in-vitro experiments,

writing original draft, draft review. **SM**: In vitro experiments, data analysis, draft review. **DGK**: In vitro experiments, draft review. **RKN**: Supervision

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