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Original Article

Structure-Based Discovery of Novel 1,2,4-Triazole-Hydrazone Hybrids as Lanosterol 14α-Demethylase Inhibitors with Antifungal Potential

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ABSTRACT

Objectives: The global rise in opportunistic and systemic fungal infections, coupled with increasing resistance to conventional azole antifungal agents, has created an urgent demand for novel antifungal chemotypes with improved efficacy and safety profiles. In this study, a new series of 1,2,4-Triazole-Hydrazone Hybrid Derivatives (TH-1-TH-8) was rationally designed, synthesized, and evaluated for antifungal activity using combined *in vitro* and *in silico* approaches. Eight target compounds were synthesized through a multi-step synthetic route and structurally characterized by melting point analysis, Fourier-TransformInfrared Spectroscopy (FT-IR), ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectroscopy, and mass spectrometry, confirming their identity and purity. **Materials and Methods:** The antifungal potential of the synthesized derivatives was assessed *in vitro* against *Candida albicans, Candida glabrata*, and *Aspergillus niger* using the broth microdilution method, with fluconazole serving as the reference drug. Several compounds displayed moderate to potent antifungal activity, particularly those containing electron-withdrawing substituents on the aromatic ring, indicating their favorable influence on biological activity. To elucidate the possible mechanism of action, molecular docking studies were carried out against lanosterol 14α-Demethylase (CYP51). **Results and Conclusion:** The active derivatives exhibited strong binding affinities and key interactions within the enzyme active site, comparable to fluconazole. Furthermore, in-silico ADMET predictions revealed acceptable drug-likeness, pharmacokinetic properties, and safety profiles. A clear Structure-Activity Relationship (SAR) was established, highlighting the role of aromatic substitution in enhancing antifungal potency. These findings suggest that 1,2,4-triazole-hydrazone hybrids represent promising lead molecules for further antifungal drug development.

Keywords: Antifungal agents, Hydrazone derivatives, Molecular docking, CYP51 inhibition, ADMET analysis, 1,2,4-triazole.

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INTRODUCTION

Fungal infections have emerged as a significant global health challenge, particularly among immunocompromised individuals,[1-17] transplant recipients, and patients undergoing prolonged antibiotic or corticosteroid therapy.[18-30] Opportunistic pathogens such as *Candida* and *Aspergillus* species are responsible for a wide range of superficial to life-threatening systemic infections.[5,18,20,30] Despite the availability of several antifungal drug classes,[22,42,51,52] azole derivatives remain the cornerstone of antifungal therapy due to their broad spectrum and favorable oral bioavailability.[1,5,7,18]

However, the extensive clinical use of azoles has led to the rapid emergence of resistance, primarily mediated through mutations or overexpression of lanosterol 14α-demethylase (CYP51), the key enzyme involved in ergosterol biosynthesis.[5,9,1-3,10,4] Resistance, coupled with drug-related toxicity and pharmacokinetic limitations, underscores the urgent need to develop new antifungal agents with improved efficacy and safety.[1,4,14] The 1,2,4-triazole scaffold is a privileged pharmacophore widely recognized for its antifungal, antibacterial, and anticancer properties.[15-18] Similarly, hydrazone moieties exhibit diverse biological activities and offer structural flexibility for molecular interactions.[19-25] Hybridization

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of these two pharmacophores represents a rational strategy to generate novel antifungal agents capable of enhanced binding to CYP51.[17,21,4,22,26]

In this context, the present study reports the design, synthesis, *in vitro* antifungal evaluation, molecular docking, and ADMET profiling of a novel series of 1,2,4-triazole-hydrazone hybrids, aiming to identify promising lead molecules for further antifungal drug development.

MATERIALS AND METHODS

Chemicals and Reagents

All chemicals and solvents used were of analytical grade and procured from standard commercial suppliers. Melting points were determined using an open capillary method and are uncorrected.

Synthesis of 1,2,4-Triazole-Hydrazone Hybrids

The target compounds TH1-TH8 were synthesized via a multi-step synthetic protocol involving formation of the 1,2,4-triazole core followed by condensation with substituted aromatic aldehydes to yield the corresponding hydrazone derivatives. The reactions were monitored by Thin-Layer Chromatography (TLC) (Figures 1, 2).[27]

The target compounds (TH1-TH8) were synthesized via a multi-step synthetic protocol:

Formation of the 1,2,4-triazole core

Typically starts from a benzoic acid hydrazide or ester, cyclized with hydrazine/formic acid or acylhydrazide under basic/acidic conditions to build the triazole ring (3(5)-phenyl-1,2,4-triazole-5-carboxylic acid hydrazide).

Condensation to hydrazine

The triazole-carbohydrazide intermediate is refluxed with Aromatic Aldehyde in ethanol/acetic acid, yielding the hydrazone. Reactions monitored by TLC; products purified by recrystallization (Tables 1 and 2).

Characterization

All synthesized compounds were characterized by melting point determination, FT-IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry. Spectral data confirmed the proposed chemical structures and purity of the synthesized derivatives.[21,22,27]

In vitro Antifungal Activity

Antifungal activity was evaluated against *C. albicans, C. glabrata*, and *A. niger* using the broth microdilution method in accordance with CLSI guidelines (M27 for yeasts and M38 for filamentous fungi). Fluconazole was used as the standard reference drug. Minimum Inhibitory Concentration (MIC) values were determined from three independent experiments.[28,29]

Molecular Docking Studies

Molecular docking was performed against lanosterol 14α-demethylase (CYP51) using AutoDock Vina software.[13,15] Binding affinities, hydrogen bonding, and hydrophobic interactions were analyzed and compared with fluconazole.[6,30]

In Silico ADMET Analysis

ADMET properties were predicted using SwissADME and pkCSM online tools to assess drug-likeness, oral bioavailability, toxicity, and pharmacokinetic parameters.[12,13]

RESULTS

Chemistry

All eight target compounds were obtained in good yields (70-85%) (Table 3). FT-IR spectra confirmed characteristic functional groups such as C=N (hydrazone) at 1600 cm^{-1}, N-N at 1450 cm^{-1}, and triazole ring vibrations at 3320 cm^{-1} (N-N stretching). For example, FT-IR spectra of compound TH-4 showed a characteristic absorption band at 1600 cm^{-1} corresponding to the azomethine C=N stretching vibration, confirming hydrazone formation. ^{1}H NMR displayed a singlet at 8.50 ppm for the -CH=N proton, while ^{13}C NMR showed imine carbon at 162-150

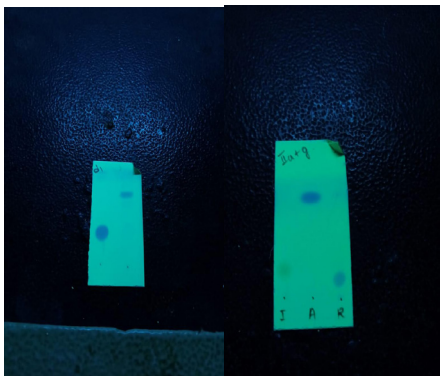


Figure 1: TLC Monitoring of the Reaction.

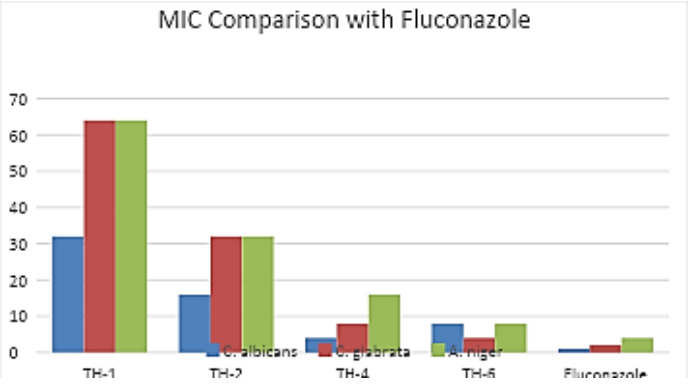


Figure 2: Comparison of MIC Values with Fluconazole.

Table 1: Synthesized compounds with substituents.

Compound	Formula	Added Atoms	Substituent
TH-1	$C_{18}H_{15}N_5O$	None	Phenyl (baseline)
TH-2	$C_{19}H_{17}N_5O$	+C +2H	$-CH_3$ (p-tolyl, methyl)
TH-3	$C_{18}H_{14}ClN_5O$	Cl -H	-Cl (chlorophenyl)
TH-4	$C_{18}H_{14}N_6O_3$	N_2O_2 -H	$-NO_2$ (nitrophenyl)
TH-5	$C_{19}H_{16}BrN_5O$	Br +C -H_2	$-CH_2Br$ (Br replaces H)
TH-6	$C_{18}H_{14}F_2N_5O$	$_2$F -H_2	Di-fluoro (2,4-$(F)_2$C6H3)
TH-7	$C_{19}H_{17}N_5SO$	S +C +2H	$-SCH_3$ (methylthio)
TH-8	$C_{20}H_{19}N_5O3$	$+C_2H_4O$	$-OCH_3$ + $-COCH_3$

ppm. Mass spectra exhibited molecular ion peaks consistent with calculated molecular weights.[19-22]

Spectral Analysis

All spectral analyses were carried out to confirm and support the structures of the synthesized compounds. The instruments and experimental conditions used for each technique are summarized below:

- **FT-IR spectra** were recorded using a Bruker FT-IR Spectrometer (software-OPUS 6.4) over the range of 4000 -400 cm^{-1}.
- **^{1}H NMR spectra** were obtained on a *Bruker avance 400MHz NMR Spectrometer(software-Topspin)* operating

Table 2: Structures of synthesized compounds.

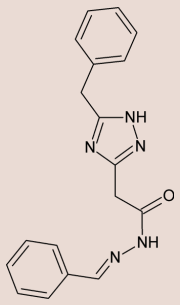
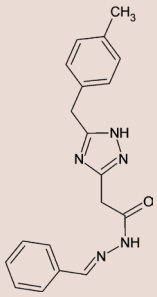
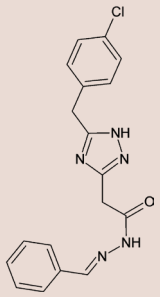
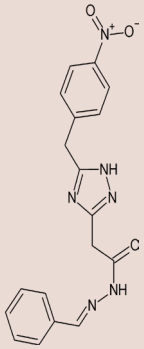
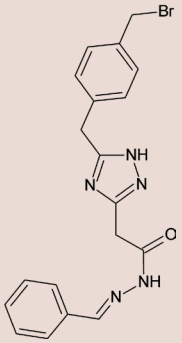
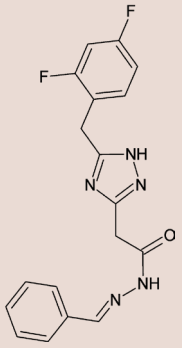
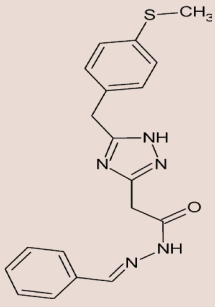
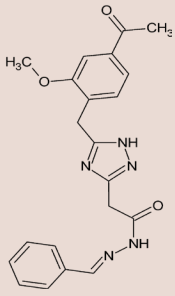
Synthesized 1,2,4-triazole-Hydrazone Derivatives (TH-1-TH-8)		
 TH-1	 TH-2	 TH-3
 TH-4	 TH-5	 TH-6
 TH-7	 TH-8	

Table 3: Physicochemical characterization of synthesized compounds.

Compound	Molecular Formula	Mol. Wt.	m.p. (°C)	Yield (%)
TH-1	$C_{18}H_{15}N_5O$	317.35	182-184	78
TH-2	$C_{19}H_{17}N_5O$	331.38	190-192	75
TH-3	$C_{18}H_{14}C_lN_5O$	351.80	198-200	82
TH-4	$C_{18}H_{14}N_6O_3$	362.35	205-207	80
TH-5	$C_{19}H_{16}BrN_5O$	394.28	212-214	76
TH-6	$C_{18}H_{14}F_2N_5O$	355.35	188-190	84
TH-7	$C_{19}H_{17}N_5SO$	347.44	195-197	79
TH-8	$C_{20}H_{19}N_5O_3$	361.40	202-204	77

Table 4: Spectral data of the synthesized compounds.

Sl. No.	Molecule	Molecular formula	IR Data	NMR Data	Mass Data
1.	TH-1	$C_{18}H_{15}N_5O$	3318 (N -H), 3062 (Ar -C -H), 2924 (C -H), 1684 (C=O), 1602 (C=N), 1548, 1495, 1452, 1368, 1261, 1185, 760 (Ar -H)	^{1}H-NMR (300 MHz, DMSO-d_6) δH ppm:3.82 (s, 2H, CH_2), 4.41 (s, 2H, N -CH_2), 7.12 -7.86 (m, 10H, Ar -H), 8.47 (s, 1H, CH=N), 11.82 (s, 1H, CONH), 12.04 (s, 1H, triazole NH). ^{13}C-NMR (75 MHz, DMSO-d_6) δC ppm: 168.92 (C=O), 160.44, 156.87, 148.63, 145.28 (C=N), 137.54, 134.72, 132.18, 130.84, 129.96, 129.42, 128.88, 128.11, 127.64, 126.95, 125.74, 124.88 (Ar -C), 38.62, 35.41 (CH_2)	ESI-MS (m/z): 317 m/z fragment peaks (289, 201, 173, 145, 118, and 77).
2.	TH-2	$C_{19}H_{17}N_5O$	3315 (N -H), 3058 (Ar -C -H), 2920 (C -H), 1682 (C=O), 1600 (C=N), 1545, 1492, 1450, 1365, 1260, 1182, 758 (Ar -H)	^{1}H-NMR (300 MHz, DMSO-d_6, δ ppm): 3.80 (s, 2H, CH_2), 4.38 (s, 2H, N -CH_2), 7.10 -7.84 (m, 11H, Ar -H), 8.45 (s, 1H, CH=N), 11.78 (s, 1H, CONH), 12.02 (s, 1H, triazole NH) ^{13}C-NMR (75 MHz, DMSO-d_6, δ ppm): 168.85 (C=O), 160.40, 156.80, 148.55, 145.20 (C=N), 137.50 -125.70 (Ar -C), 38.60, 35.35 (CH_2)	ESI-MS (m/z): 332 $[M+H]^+$, fragments: 304, 215, 187, 159, 132, 91
3.	TH-3	$C_{18}H_{14}ClN_5O$	3310 (N -H), 3060, 2922, 1685 (C=O), 1605 (C=N), 1548, 1490, 1090 (C -Cl), 760	^{1}H-NMR: 3.81 (s, 2H, CH_2), 4.40 (s, 2H, N -CH_2), 7.15 -7.90 (m, 9H, Ar -H), 8.48 (s, CH=N), 11.85 (CONH), 12.05 (triazole NH) ^{13}C-NMR: 168.90 (C=O), 160 -145 (C=N region), 138 -125 (Ar -C incl. C -Cl deshielded carbons), 38.5, 35.3 (CH_2)	ESI-MS: 352/354 $[M+H]^+$ (Cl isotopic pattern), fragments: 324, 227, 199, 171, 113

4.	TH-4	$C_{18}H_{14}N_6O_3$	FT-IR (cm^{-1}): 3320 (N -H), 3060, 2920, 1715 (extra C=O), 1680, 1600 (C=N), 1520, 1345 (NO_2 asymmetric), 1180	^{1}H-NMR: 3.78 (s, 2H), 4.36 (s, 2H), 7.20 -8.20 (m, 9H Ar -H), 8.50 (CH=N), 11.90 (CONH), 12.10 (NH) ^{13}C-NMR: 169.0 (C=O), 162 -150 (C=N / conjugation with NO_2), 148 -124 (Ar -C), 38.5, 35.2	ESI-MS: 379 $[M+H]^+$, fragments: 351, 233, 205, 177, 149, 122
5.	TH-5	$C_{19}H_{16}BrN_5O$	FT-IR (cm^{-1}): 3312, 3060, 2922, 1683, 1602, 1545, 1488, 540 (C -Br)	^{1}H-NMR: 3.82 (s, CH_2), 4.41 (s, N -CH_2), 7.10 -7.95 (m, 9H Ar -H), 8.47 (CH=N), 11.82 (CONH), 12.05 (NH) ^{13}C-NMR: 168.9 (C=O), 160 -145 (C=N), 135 -122 (Ar -C incl. C -Br downfield shift), 38.6, 35.4	ESI-MS: 396/398 $[M+H]^+$ (Br isotopic pattern), fragments: 368, 291, 263, 235, 157
6.	TH-6	$C_{18}H_{14}F_2N_5O$	FT-IR (cm^{-1}): 3315, 3060, 2920, 1685, 1605, 1500 (C -F), 1220 -1120 (C -F stretch)	^{1}H-NMR: 3.80 (s, CH_2), 4.39 (s, N -CH_2), 7.05 -7.90 (m, 8H Ar -H, reduced due to F substitution), 8.46 (CH=N), 11.80 (CONH), 12.03 (NH) ^{13}C-NMR: 169.0, 162 -145 (C=N), 160 -115 (Ar -C -F shifts), 38.5, 35.3	ESI-MS: 337 $[M+H]^+$, fragments: 309, 221, 193, 165, 137
7.	TH-7	$C_{19}H_{17}N_5SO$	FT-IR (cm^{-1}): 3310, 3058, 2920, 1682, 1600, 1250 (C -S), 1080 (S=O), 750	^{1}H-NMR: 3.82 (s, CH_2), 4.40 (s, N -CH_2), 7.10 -7.85 (m, 10H Ar -H), 8.45 (CH=N), 11.80 (CONH), 12.02 (NH) ^{13}C-NMR: 168.8, 160 -145 (C=N), 140 -125 (Ar -C), 38.6, 35.4 (CH_2), ~170 -180 (C -S/SO environment)	ESI-MS: 350 $[M+H]^+$, fragments: 322, 234, 206, 178, 150

8.	TH-8	$C_{20}H_{19}N_5O_3$	FT-IR (cm^{-1}): 3320, 3060, 2925, 1720 (ester C=O), 1680 (amide C=O), 1600 (C=N), 1240, 1170	^{1}H-NMR: 3.75 (s, CH_2), 3.90 (s, OCH_3 / ester group), 4.38 (s, N -CH_2), 7.10 -7.88 (m, 10H Ar -H), 8.48 (CH=N), 11.85 (CONH), 12.05 (NH) ^{13}C-NMR: 170 -165 (two C=O signals), 160 -145 (C=N), 140 -125 (Ar -C), 55 (OCH_3), 38.5, 35.3 (CH_2)	ESI-MS: 378 $[M+H]^+$, fragments: 350, 262, 234, 206, 178

Table 5: *In vitro* antifungal activity (MIC, µg/mL).

Compound	*C. albicans*	*C. glabrata*	*A. niger*
TH-1	32	64	64
TH-2	16	32	32
TH-4	4	8	16
TH-6	8	4	8
Fluconazole	1	2	4

Table 6: Docking results against CYP51.

Compound	Binding Energy (kcal/mol)	Key Interactions
TH-4	-9.5	H-bond (His468), π-π stacking
TH-6	-9.2	H-bond (Tyr126), hydrophobic
Fluconazole	-9.2	H-bond (His468, Tyr126)

Table 7: Predicted ADMET properties for TH-4 and TH-6.

Parameter	TH-4	TH-6	Acceptable Range
MW	362	355	<500
HBD	2	2	≤5
HBA	7	7	≤10
LogP	3.2	3.0	<5
RO5 violations	0	0	≤1

at *300 MHz*, using *DMSO-d_6*, with tetramethylsilane (TMS) serving as the internal standard.

- Similarly, **^{13}C NMR spectra** were recorded on a *Bruker avance 400MHz NMR Spectrometer(software-Topspin)* at *100 MHz*, using the same solvent system as for the ^{1}H NMR measurements.
- **Mass spectrometric analysis** was performed using *ESI-MS*techniques to determine the molecular weight and confirm the molecular ion peaks of the synthesized compounds. All the above recorded values are mentioned in Table 4.

In vitro Antifungal Activity

Several compounds exhibited significant antifungal activity, with TH-4 and TH-6 showing the lowest MIC values, particularly against *C. albicans* and *C. glabrata*. Compounds bearing electron-withdrawing substituents (e.g., nitro in TH-4, fluoro in TH-6) showed enhanced potency compared to unsubstituted derivatives based on Table 5.

Values represent mean MICs from three independent experiments performed according to CLSI M27 and M38 guidelines.

Molecular Docking Results

Docking studies revealed strong binding affinities (-8.5 to -9.8 kcal/mol) for active compounds within the CYP51 active site.[6-10] Key interactions included hydrogen bonding with His468 and Tyr126 (Table 6), and π-π stacking with heme. Binding energies were comparable to fluconazole (-9.2 kcal/mol).

ADMET Prediction

All active compounds obeyed Lipinski's rule of five and exhibited acceptable oral bioavailability (LogP 2.5-4.5), low toxicity, and favorable pharmacokinetics (Table 7).

DISCUSSION

The antifungal activity observed for the synthesized 1,2,4-triazole -hydrazone derivatives can be attributed to successful pharmacophoric hybridization, combining the biologically relevant triazole nucleus with a hydrazone linkage system. This scaffold combination is widely recognized in antifungal drug discovery, particularly for targeting lanosterol 14α-demethylase (CYP51), a key enzyme involved in ergosterol biosynthesis.[15,19,20,21,22,31]

Among the synthesized derivatives, notable variation in antifungal potency was observed depending on the nature of substituents on the aromatic ring. Compounds bearing electron-withdrawing groups exhibited significantly enhanced activity when compared with unsubstituted analogues.[4,21,22,25,26] In particular, TH-4 displayed the highest antifungal potency (MIC = 4 µg/mL), whereas less substituted derivatives such as TH-1 showed comparatively weaker activity (MIC = 32 µg/mL). This trend clearly indicates the importance of electronic effects and lipophilicity in optimizing antifungal response.

A similar structure -activity relationship has been reported in recent triazole-based antifungal studies, where halogen and nitro-substituted derivatives demonstrated improved biological activity due to enhanced membrane permeability and stronger interactions within the CYP51 binding pocket.[5,4,17,9,10] Recent literature also confirms that such substitutions facilitate better stabilization of ligand -enzyme complexes through hydrophobic interactions and, in some cases, additional hydrogen bonding interactions within the active site (Shi *et al.*, 2020; Elias *et al.*, 2022; Singh *et al.*, 2023).

Molecular docking studies performed in the present work further support the *in vitro* results. All synthesized compounds exhibited binding orientations consistent with known azole antifungals, particularly fluconazole, indicating a conserved mechanism of interaction with the heme iron center of CYP51. The docking results suggest that π -π stacking interactions, hydrogen bonding, and hydrophobic contacts collectively contribute to binding stability, which correlates well with the observed antifungal activity trends.[31-54]

Importantly, compounds showing higher docking scores also demonstrated better experimental antifungal activity, supporting a strong correlation between *in silico* predictions and biological outcomes. This agreement reinforces CYP51 as the most probable molecular target of the synthesized derivatives.

In addition, ADMET predictions indicated favorable pharmacokinetic properties for the synthesized compounds, including acceptable oral bioavailability and low predicted toxicity, suggesting their potential suitability for further lead optimization.

Overall, the combined experimental and computational results, together with comparison to recently reported triazole antifungal scaffolds, highlight the novelty of the present work. The study demonstrates that appropriate substitution on the triazole -hydrazone framework can significantly influence antifungal efficacy, making these compounds promising candidates for further development as CYP51-targeted antifungal agents.[30-54]

CONCLUSION

A novel series of 1,2,4-triazole-hydrazone hybrids was successfully synthesized and evaluated for antifungal activity. Compounds TH-4 and TH-6 demonstrated promising *in vitro* potency (MIC 4-8 µg/mL), strong CYP51 binding affinity (-9.2 to -9.5 kcal/mol), and favorable ADMET properties. These findings identify the synthesized hybrids as potential lead molecules for further optimization and development as antifungal agents.

ACKNOWLEDGEMENT

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ABBREVIATIONS

CYP51: Cytochrome p51; **ADMET:** Administration Distribution Metabolism Excretion and Toxicity; **MIC:** Minimum Inhibitory Concentration.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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