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Synthesis of Ether and Thioether Derivatives Containing a 1,2,4-Triazole Ring: Antioxidant Activity and Antimicrobial Properties

Alhamzah D. Hameed

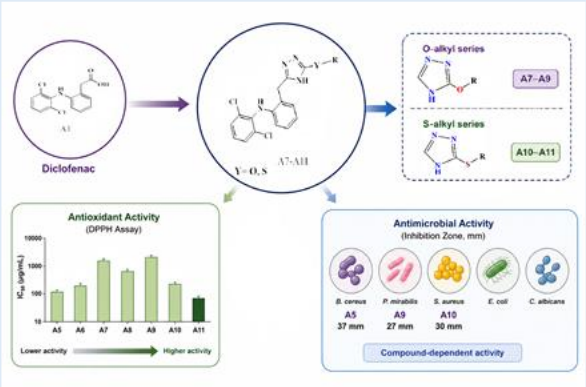
Department of Renewable Energy Science, College of Energy and Environmental Sciences, Al-Karkh University of Science, Baghdad, Iraq

Abstract

Introduction.The 1,2,4-triazole ring's structural adaptability and wide range of documented biological activities make it a significant heterocyclic scaffold in medicinal chemistry. Objectives. This study synthesized a series of 1,2,4-triazole ether and thioether derivatives (designated A5–A11) from diclofenac and assessed their antimicrobial and antioxidant properties. Materials and Methods. Diclofenac sodium was converted to diclofenac acid and its methyl ester in the synthetic sequence. This was followed by a reaction with semicarbazide or thiosemicarbazide, cyclization to the corresponding 1,2,4-triazole derivatives, and then alkylation with allyl bromide, benzyl chloride, or isopentyl bromide. FTIR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy were used to characterize the synthesized compounds.The DPPH radical-scavenging assay was used to measure antioxidant activity at 6.25–100 µg/mL. Results.Compound A11 had the lowest reported IC_{50} value (46.1 µg/mL), followed by A5 (68.32 µg/mL) and A9 (2039 µg/mL). Antimicrobial screening revealed compound-dependent activity against Bacillus cereus, Candida albicans, Staphylococcus aureus, Proteus mirabilis, and Escherichia coli. The largest inhibition zones were produced by A5 against B. cereus (37 mm), A9 against P. mirabilis (27 mm), and A10 against S. aureus (30 mm). Conclusions.The findings show significant differences in biological activity between the synthesized derivatives and offer initial structure-activity data for additional research on 1,2,4-triazole ether and thioether derivatives.

1,2,4-triazole;
Ether;
Thioether;
Diclofenac Derivatives;
Antioxidant Activity;
Antimicrobial Activity.

Graphical Abstract



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Faculty of Science, ATBU Bauchi

Corresponding Author: Alhamzah D. Hameed, Department of Renewable Energy Science, College of Energy and Environmental Sciences, Al-Karkh University of Science, Baghdad, Iraq. Email: alhamzah.dheyaa@kus.edu.iq © 2026 Faculty of Science, ATBU Bauchi. All rights reserved

INTRODUCTION

Because of its structural adaptability and the wide range of biological activities reported for its derivatives, the 1,2,4-triazole heterocycle is an important scaffold in medicinal chemistry[1-3]. Numerous nitrogen atoms in the ring can engage in hydrogen bonding and other molecular interactions, and substitution at various locations offers chances to alter the compounds physicochemical and biological characteristics. An established method for altering molecular polarity, lipophilicity, steric characteristics, and conformational behavior is the integration of ether and thioether functionalities into heterocyclic structures[4, 5].

Because sulfur has a larger atomic radius and greater polarizability than oxygen, derivatives containing sulfur can differ significantly from their oxygen counterparts. These variations may affect how molecules are recognized and interact with macromolecular targets or biological membranes.The biological properties of 1,2,4-triazole derivatives can be further altered by alkyl substitution. Molecular size, hydrophobicity, conformational flexibility, and the spatial environment surrounding the heterocyclic nucleus are all influenced by the type of attached alkyl group[6, 7]. Thus, structurally distinct substituents on a common heterocyclic framework can be systematically compared to yield valuable preliminary structure-activity information. Numerous pathological processes have been linked to oxidative stress, which is linked to an imbalance between the production of reactive oxygen species and endogenous antioxidant defenses. Therefore, a number of chemical tests, such as the ferric-reducing antioxidant power measurements and the DPPH radical-scavenging assay, have been used to examine the antioxidant characteristics of heterocyclic compounds [8, 9].The ongoing emergence of antimicrobial resistance makes the development of new antimicrobial compounds crucial. Derivatives of 1,2,4-triazole, especially those containing sulfur, have been studied against fungi and both Gram-positive and Gram-negative bacteria[10-12]. Despite the synthesis of numerous 1,2,4-triazole derivatives, there is still little comparative analysis of allyl-, benzyl-, and isopentyl-substituted derivatives within a common structural framework. These substituents offer a chance to investigate their impact on biological reactions because they vary in aromaticity, steric requirements, hydrophobicity, and conformational flexibility.

MATERIALS AND METHODS

Instrumentation

Chemicals and instrumentation. All chemicals and reagents used in the synthesis were obtained from Merck, Fluka, and CDH Chemical Companies and were used as received unless otherwise stated. The synthesized products were characterized by melting-point determination and Fourier-transform infrared (FT-IR) spectroscopy. FT-IR spectra were recorded using a Shimadzu spectrometer at the University of Baghdad, Iraq. Thin-layer chromatography (TLC) was used to monitor the progress of each synthetic reaction. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded using a Bruker 400 MHz spectrometer at the University of Basrah, Iraq, with chemical shifts reported in parts per million (δ, ppm).

Synthesis of the chemical compound

All solvents and reagents were obtained from commercial suppliers and used without further purification unless otherwise stated.

Synthesis of Diclofenac Acid (A1)[13].

Diclofenac sodium (5 g) was dissolved in distilled water with continuous stirring. A 4 N solution of hydrochloric acid was added gradually until complete precipitation of diclofenac acid was achieved. The precipitated solid was collected by filtration, washed repeatedly with distilled water to remove residual acid, and dried at room temperature. The isolated compound A1 was obtained as

a white solid with a melting point of 183–185 °C and an isolated yield of 95%.

Synthesis of Diclofenac Methyl Ester (A2)[14].

Compound A1 (0.0135 mol, 4 g) was dissolved in methanol (20 mL), and concentrated sulfuric acid (5 mL) was added dropwise. The reaction mixture was refluxed for 8 h. After cooling, the reaction mixture was poured onto crushed ice. The precipitated product was collected by filtration, washed with aqueous sodium bicarbonate followed by distilled water, and recrystallized from ethanol to afford compound A2. Compound A2 was obtained as a white solid with a melting point of 78–80 °C and an isolated yield of 84%.

Synthesis of Carboxamide and Carbothioamide Derivatives (A3 and A4)[15].

Compound A2 (0.01 mol) was reacted separately with semicarbazide (0.0133 mol, 1 g) or thiosemicarbazide (0.0109 mol, 1 g) in tetrahydrofuran (30 mL). A few drops of piperidine were added, and the reaction mixture was refluxed for 6 h. After cooling, the precipitated products were collected by filtration, washed with ethanol, and recrystallized to afford compounds A3 and A4.

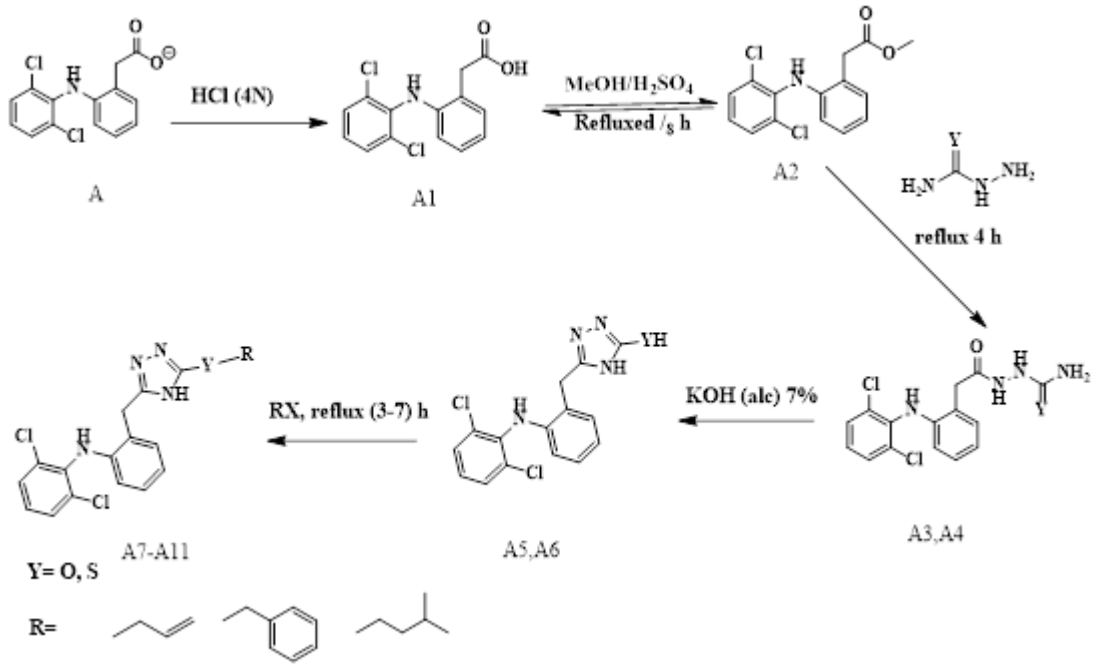
Synthesis of 1,2,4-Triazole Derivatives (A5 and A6)[16].

Compounds A3 and A4 were separately suspended in 7% alcoholic potassium hydroxide solution (10 mL) and refluxed for 10 h. The reaction mixtures were cooled and acidified to pH 6 using 10% hydrochloric acid. The resulting solids were collected by filtration, washed with water, dried, and recrystallized from ethanol to afford compounds A5 and A6.

The resulting compounds were assigned as the corresponding 1,2,4-triazole-5-ol (A5) and 1,2,4-triazole-5-thiol (A6) derivatives based on the spectroscopic data reported below.

Synthesis of Ether and Thioether Derivatives (A7–A11)[17].

Potassium hydroxide (0.002 mol, 0.112 g) was added to the appropriate triazole precursor (0.001 mol) in tetrahydrofuran (10 mL), and the mixture was refluxed for 2 h. The appropriate alkyl halide (0.003 mol)—allyl bromide, benzyl chloride, or isopentyl bromide—was then added, and refluxing was continued for 7–10 h. After cooling, the precipitated product was collected by filtration, washed three times with diethyl ether, and recrystallized from methanol. Reaction progress was monitored by thin-layer chromatography using petroleum ether/ethyl acetate (3:7, v/v). Column chromatography was used when additional purification was required. All compounds as shown in (Scheme1), and Physical properties as shown in Table (1).



Scheme (1): Synthetic route for the target compounds

Table 1: Physical properties of compounds A1–A11

Yield (%)	m.p.	Color	Molecular weight (g/ mol^{-1})	Compound
95	183–185 °C	White	296.15	A1
84	78–80 °C	White	310.17	A2
72	190–192 °C	Pale yellow	353.20	A3
78	178–180 °C	Yellow	369.26	A4
74	162–164 °C	White	335.19	A5
59	134–136 °C	Light yellow	351.25	A6
73	106–108 °C	Brown	375.25	A7
65	234–236 °C	Light brown	425.31	A8
54	148–150 °C	Off-white	405.32	A9
58	Oil	Yellow	391.31	A10
58	Oil	Pale yellow	441.37	A11

Assay for DPPH Radical-Scavenging[18].

The DPPH free-radical-scavenging assay was used to assess the antioxidant activity of compounds A5–A11. At concentrations of 100, 50, 25, 12.5, and 6.25 µg/mL, the compounds were tested. Concentration–response curves were created using absorbance measurements, and IC_{50} values were derived from these curves.

Activity Against Microbes[19].

By calculating the zones of inhibition against Escherichia coli, Proteus mirabilis, Staphylococcus aureus, Bacillus cereus, and Candida albicans, the antimicrobial activity of compounds A5–A11 was assessed. Millimeters were used to measure the inhibition-zone diameters.

The number of microbial strains, inoculum density, assay medium, compound concentration, controls, incubation conditions, and number of replicates are all inadequately described in the original manuscript. Before submission, the laboratory protocol should be updated with these experimental details.

RESULTS

Synthetic Route

(A1), then esterification to produce A2. Intermediates A3 and A4 were produced when A2 subsequently reacted with either semicarbazide or thiosemicarbazide. These intermediates underwent alkaline cyclization to yield the corresponding 1,2,4-triazole derivatives A5 and A6. A5 was further alkylated with isopentyl bromide, benzyl chloride, and allyl bromide to produce A7, A8, and A9, respectively. A10 and A11 were also produced by alkylating A6 with benzyl chloride and allyl bromide. The O-alkyl derivatives A7–A9 and the S-alkyl derivatives A10–A11 were the two structural series that made up the synthesized compounds.

FTIR Characterization

O–H, N–H, and carboxylic acid C=O stretching vibrations were responsible for the absorptions in A1's FTIR spectrum at 2925 cm^{-1}, 3323 cm^{-1}, and 1700 cm^{-1}, respectively. C–Cl stretching was identified as the cause of the bands at 769 and 742 cm^{-1}. The broad carboxylic acid O–H absorption vanished after esterification to A2, the carbonyl band moved to 1731 cm^{-1}, and a new C–O absorption emerged at 1240 cm^{-1}. For A3, absorptions at 3427 and 3323 cm^{-1} corresponded to NH_2 and N–H stretching, while the bands at 1718 and 1695 cm^{-1} were assigned to carbonyl groups.

Aromatic C=C, N–N, and C–N absorptions occurred at approximately 1573/1505, 1454, and 1303 cm^{-1}, respectively. For A4, the amide C=O and C=S absorptions occurred at 1695 and 1271 cm^{-1}, respectively. The FTIR spectrum of A5 displayed O–H absorption at 3517 cm^{-1} and N–H absorptions at 3433 and 3323 cm^{-1}.

The triazole C=N band appeared at 1645 cm^{-1}. In A6, no O–H absorption was observed, whereas N–H bands occurred at 3411 and 3295 cm^{-1} and the C=N band at 1629 cm^{-1}. The spectra of A7–A11 showed triazole N–H absorptions at 3427–3434 cm^{-1} and additional N–H bands around 3222–3323 cm^{-1}. C=N absorptions occurred between 1608 and 1693 cm^{-1}. The O-alkyl derivatives A7–A9 exhibited C–O–C absorptions at 1174–1176 cm^{-1}, whereas these bands were absent in A10 and A11. Tables 3 and 4 summarize the selected FTIR data for A3–A4 and A7–A11, respectively.

Table 3: Selected FTIR data for A3 and A4

ν C=S	ν C–N	ν N–N	ν C=C (Ar.)	ν C=O	ν C–H (aliph.)	ν C–H (Ar.)	ν N–H	ν NH_2	Compound
—	1303	1454	1573, 1505	1718, 1695	2925	3087	3323	3427	A3
1271	1301	1454	1573, 1508	1695	2927	3078	3323	3433	A4

Table 4: Selected FTIR data for A7–A11

ν C–O–C	ν C–N	ν N–N	ν C=C (Ar.)	ν C=N	ν C–H (aliph.)	ν C–H (Ar.)	ν N–H	ν N–H (triazole)	Compound
1176	1315	1440	1566	1608	2923	3053	3222	3423	A7
1159	1321	1452	1583	1693	2921	3070	3323	3434	A8
1174	1317	1440	1566	1608	2923	3055	3228	3427	A9
—	1373	1452	1573	1631	2968	3074	3323	3431	A10
—	1330	1457	1566	1608	2923	3055	3228	3427	A11

^{1}H-NMR Characterization

The ^{1}H-NMR spectra of A7–A11 contained signals corresponding to the triazole NH, aromatic protons, secondary amine, methylene bridge, and introduced alkyl groups. For A7, the triazole NH appeared at δ 12.76 ppm, aromatic protons at δ 7.55–6.25 ppm, allylic signals at δ 5.98–5.88 and 5.31–5.21 ppm, and O–CH_2 at δ 4.61 ppm. A8 showed the triazole NH at δ 12.74 ppm, aromatic signals at δ 7.54–6.29 ppm, and O–CH_2 at δ 4.66 ppm. A9 displayed the triazole NH at δ 12.74 ppm, aromatic resonances at δ 8.23–6.28 ppm, O–CH_2 at δ 4.44 ppm, and isopentyl signals at δ 1.62, 1.46, and 0.85 ppm. A10 exhibited allyl resonances at δ 5.94–5.79 and 5.08–5.02 ppm, with the triazole NH at δ 10.24 ppm. A11 showed the triazole NH at δ 10.55 ppm and a benzylic S–CH_2 signal at δ 3.95 ppm.

^{13}C-NMR Characterization

The ^{13}C-NMR spectra of A7–A11 showed signals attributable to the triazole C=N carbons and aromatic carbon framework. For A7, the triazole C=N carbons occurred at δ 151.43 and 143.30 ppm, while the O–CH_2 and benzylic CH_2 signals appeared at δ 66.45 and 38.27 ppm, respectively. A8 showed C=N signals at δ 156.50 and 150.22 ppm and an O–CH_2 resonance at δ 66.51 ppm. For A9, the triazole C=N signals appeared at δ 157.35 and 143.13 ppm, with an O–CH_2 resonance at δ 75.94 ppm. A10 showed triazole C=N signals at δ 165.90 and 161.68 ppm, whereas A11 showed corresponding signals at δ 160.15 and 153.22 ppm. The original assignment of the A11 signal at δ 66.51 ppm as O–CH_2 requires verification against the original spectrum because A11 is assigned structurally as an S-benzyl derivative.

Antioxidant Activity

The DPPH radical-scavenging activity of A5–A11 was evaluated at concentrations ranging from 6.25 to 100

µg/mL. The IC_{50} values were 68.32 µg/mL for A5, 119.8 µg/mL for A6, 1106 µg/mL for A7, 464.8 µg/mL for A8, 2039 µg/mL for A9, 161.7 µg/mL for A10, and 46.1 µg/mL for A11. Thus, A11 showed the lowest IC_{50} value among the tested compounds. Table **5** presents the complete DPPH dataset.

Table 5: DPPH radical-scavenging activity of A5–A11

R^2	IC_{50} (µg/mL)	Hill slope	6.25 µg/mL	12.5 µg/mL	25 µg/mL	50 µg/mL	100 µg/mL	Compound
0.9672	68.32	0.6313	20.00	26.87	29.90	46.06	57.17	A5
0.9080	119.8	0.3633	28.28	30.51	32.53	40.40	51.31	A6
0.9150	1106	0.2203	24.85	27.27	30.30	31.11	38.79	A7
0.8098	464.8	0.2228	30.71	28.89	32.93	35.56	44.24	A8
0.9498	2039	0.2221	22.22	24.65	26.87	28.89	35.15	A9
0.7696	161.7	0.2928	30.91	31.72	34.55	36.36	51.31	A10
0.8242	46.1	0.4406	33.13	37.17	37.78	45.86	64.85	A11

Antimicrobial Activity

The synthesized compounds showed variable inhibition-zone diameters against the tested microorganisms. A5 produced the largest inhibition zone against B. cereus (37 mm). A9 showed the largest response against P. mirabilis (27 mm), whereas A10 gave the largest inhibition zone against S. aureus (30 mm). A11 produced a 25-mm inhibition zone against S. aureus. The inhibition zones against C. albicans ranged from 10 to 15 mm. The complete results are presented in Table **6**.

Table 6: Antimicrobial activity of A5–A11

C. albicans	*B. cereus*	*S. aureus*	*P. mirabilis*	*E. coli*	Compound
15	37	11	20	16	A5
10	10	12	15	13	A6
12	34	10	16	11	A7
10	35	12	21	10	A8
14	15	20	27	14	A9
10	14	30	15	12	A10
14	13	25	14	14	A11

DISCUSSION

Synthetic Sequence and Structural Verification

The suggested progression from diclofenac-derived intermediates to the final 1,2,4-triazole derivatives is

supported by the spectroscopic results taken together. The disappearance of the carboxylic acid O–H absorption, the displacement of the carbonyl band, and the emergence of an ester C–O absorption all support the conversion of A1 to A2. The appearance of distinctive triazole C=N absorptions and the corresponding modifications in O–H, N–H, and C=S functionalities are consistent with the subsequent formation of A5 and A6. Alkylation of the triazole derivatives is further supported by the spectral behavior of A7–A11. Specifically, the C–O–C bands seen in A7–A9 are consistent with O-alkylation, while their absence in A10 and A11 is consistent with the formation of S-alkyl derivatives.

Structural Impacts and Antioxidant Activity

The antioxidant findings show that structural alteration of the triazole framework significantly influences the DPPH response. Based on its lowest IC_{50} value (46.1 μg/mL), A11 showed the strongest radical-scavenging response, followed by A5 (68.32 μg/mL). The O-alkyl derivatives A7–A9, on the other hand, displayed significantly higher IC_{50} values. The comparison of A5 and its O-alkylated derivatives shows that the measured radical-scavenging response is significantly altered when the oxygen-containing triazole framework is modified. However, since the current dataset does not identify a single structural parameter responsible for the observed variation, the differences between A7–A9 cannot be reliably attributed to alkyl-chain size alone.A particularly useful comparison is given by the S-alkyl series. A10 had an IC_{50} of 161.7 μg/mL, while A11 had a significantly lower IC_{50} of 46.1 μg/mL when the allyl substituent in A10 was replaced with a benzyl group. Although more analogs would be needed to establish a conclusive SAR, this observation suggests that substituent identity and the resulting molecular environment may influence antioxidant response. A helpful initial comparison is provided by the lower IC_{50} of A11 in comparison to the 227 μg/mL value reported by Gultekin for another class of 1,2,4-triazoles. However, such IC_{50} values should not be interpreted as directly equivalent due to variations in assay conditions and experimental protocols.

Compound-Dependent Reaction and Antimicrobial Activity

Additionally, the antimicrobial profile differed based on the microorganism and compound structure. A10 showed the biggest inhibition zone against S. aureus, while A5 showed the strongest response against B. cereus. Even though it was less than that of A10, A11's activity against S. aureus was noteworthy. These variations suggest that a consistent antimicrobial response is not produced by structural alteration of the triazole framework. Although the current inhibition-zone data are insufficient to establish a quantitative structure–activity relationship, the comparison between the O- and S-containing derivatives indicates that the heteroatom involved in alkylation may influence the observed biological profile.

Initial Structure–Activity Connections

When combined, the biological data yield a number of initial SAR observations. The parent triazole A5 has the biggest inhibition zone against B. cereus and comparatively high DPPH activity. A significant decrease in DPPH activity is linked to O-alkylation to produce A7–A9, though the strength of this effect varies depending on the alkyl substituent. A10 and A11 in the sulfur-containing series show how altering the alkyl substituent can significantly change the biological response. The allyl-containing A10 demonstrated the greatest inhibition zone against S. aureus, while the benzyl-containing A11 displayed the strongest DPPH activity of the series. Therefore, the structural trend of antioxidant and antimicrobial activities differs.

CONCLUSIONS

Esterification, the creation of semicarbazide and thiosemicarbazide intermediates, triazole cyclization, and subsequent alkylation were the steps in the synthesis of a series of 1,2,4-triazole ether and

thioether derivatives derived from diclofenac. O-allyl (A7), O-benzyl (A8), O-isopentyl (A9), S-allyl (A10), and S-benzyl (A11) derivatives were among the final derivatives.

The suggested structures were supported by spectroscopic characterization using FTIR, ^{1}H-NMR, and ^{13}C-NMR; however, the reported ^{13}C-NMR assignment of one signal in A11 should be checked against the original spectrum.Significant variations in antioxidant response were found by the DPPH assay, with A11 exhibiting the lowest reported IC_{50} value (46.1 µg/mL), followed by A5 (68.32 µg/mL). Additionally, compound- and microorganism-dependent activity was shown by antimicrobial screening. The biggest inhibition zones were displayed by A5 against B. cereus, A9 against P. mirabilis, and A10 against S. aureus. The findings suggest that altering the 1,2,4-triazole framework with various alkyl groups linked to oxygen and sulfur can affect antimicrobial and antioxidant reactions. The current results should be considered preliminary, though. To establish more reliable structure–activity relationships, more research involving standardized antimicrobial susceptibility testing, MIC/MBC/MFC determination, replication and statistical analysis, and additional mechanistic experiments is needed.

DATA AVAILABILITY

The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request, subject to institutional and ethical restrictions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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