***Research Article***

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# Design, synthesis, molecular docking and biological evaluation of a novel β-lactam derivative with anti-breast cancer activity

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ABSTRACT

This study presents the synthesis and characterization of Azo, Schiff base, and novel β-lactam derivatives. The Azo derivative (A1) was synthesized by coupling the diazonium salt prepared by dissolving 2-(aminomethyl)aniline in acidic medium at (0-5)°C with 4,5-diphenyl-1H-imidazole. The Schiff base derivative (S1) was then synthesized by reacting the Azo derivative prepared in the previous step with 3-phenyl-1H-pyrazole-4-carbaldehyde. Finally, the β-lactam derivative (B1) was prepared by reacting the Schiff base derivative prepared in the second step with triethylamine and Chloroacetyl chloride. The structural characterization of the synthesized compounds was carried out using (FT-IR), ($^{1}$H-NMR) and ($^{13}$C-NMR) spectroscopy. The molecular docking of the beta-lactam derivative against the breast cancer-associated MCF-7 protein was studied, revealed a binding affinity of (−8.78kcal/mol), indicating a strong interaction between the ligand and the target protein. Furthermore, the root-mean-square deviation (RMSD) value of (2.40Å) suggests a stable and consistent binding conformation within the active site indicating strong potential as an anticancer agent. Biological assays demonstrated selective toxic activity against MCF-7 breast cancer cells with an $IC_{50}$ of (102.2µg/mL), while showing less toxicity to normal WRL-68 cells ($IC_{50}$ = 230.1µg/mL).

## 1. Introduction

Azo compounds are identified by the presence of the azo group (–N=N–), where the nitrogen atoms are connected to organic parts, R and R′, which can be either alkyl or aryl groups, affecting the molecule's electronic and steric properties. The -N=N- segment, known as the azo group, serves as a bridge connecting a variety of different groups, whether aliphatic or aromatic. When the azo group links aromatic groups, the resulting compounds are known as aromatic azo dyes, which are highly valued for their exceptional stability [1-3]. The remarkable stability of aromatic azo compounds is largely due to the strong double bond of the azo group (-N=N-) and the nature of the groups attached to it. In addition to their widespread usage in medicine and pharmacy, azo compounds are also used as cytotoxic chemicals and antiviral, antifungal, antibacterial, and anticancer agents [4-6].

condensation process between primary amines (which can be either aliphatic or aromatic) and aldehydes or ketones (which can likewise be either aliphatic or aromatic) [7,8]. Schiff base derivatives are well known for their remarkable biological activity and are safe and efficient therapeutic agents, especially when used to treat cancer and bacterial infections. Numerous Schiff base complexes have a variety of pharmacological and biological characteristics [9,10]. Specifically, the antibacterial, antifungal, anti-inflammatory, analgesic, antituberculosis, and antioxidant [11,12].

Schiff bases are a type of chemical compound that are distinguished by the presence of an azomethine group (-CH=N-) [7]. Typically, an acid catalyzes the β-lactam, which refers to a type of amide ring structure named for the position of the nitrogen atom attached to the β-carbon of the carbonyl group and is also known as azetidin-2-one [13]. Numerous compounds containing the beta-lactam ring demonstrate antibacterial properties by inhibiting bacterial cell wall synthesis [14]. Additionally, aromatic compounds incorporating multiple beta-lactam rings

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have been found to possess anticancer, anti-inflammatory, and other biological activities. The beta-lactam ring forms a core component of many important compounds, particularly antibiotics such as penicillin, cephalosporins, carbapenems, and clavams, which are widely used to treat infections [15]. These antibiotics are collectively termed beta-lactam antibiotics, and their differences arise primarily from the structure of the ring system attached to the beta-lactam core [16]. Therefore, the study and synthesis of azole-based derivatives represent an important approach for the development of new compounds with promising biological properties [17-20]. In this work, a new series of azole-based derivatives were designed, synthesized, and evaluated for their biological activity.

## 2. Materials and Methods

The highly pure chemicals used in this study are sodium hydroxide, 4,5-diphenyl-1H-imidazole, and 3-phenyl-1H-pyrazole-4-carbaldehyde (Germany, Sigma Aldrich); dry benzene (UK, Avonchem); 2-(aminomethyl)aniline, chloroacetyl chloride, sodium nitrite, and triethylamine (India, Thomas Baker); glacial acetic acid, and hydrochloric acid (India, Himedia); and absolute ethanol (Spain, Scharlau).

Fourier-transform infrared (FT-IR) spectra in the range of 4000–400 $cm^{-1}$ were obtained using a Bruker TENSOR 27 spectrometer with the KBr pellet method at the University of Al-Qadisiyah, Iraq.

The 1H-NMR and 13C-NMR spectra were recorded in ppm using a Bruker Ultra Shield 300MHz spectrometer, employing DMSO-$d_6$ as the solvent. All measurements were conducted at Tehran University, Iran. Melting points were determined using an electrothermal apparatus (Stuart, UK).

### 2.1. Experimental

**Synthesis of Azo derivative (A1) (2-((4,5-diphenyl-1H-imidazol-2-yl)diazenyl)phenyl)methanamine**

After dissolving 0.004 moles of 2-(aminomethyl)aniline in 4 mL of HCl and 30 mL of distilled water, the mixture was cooled to 0–5°C and stirred constantly for 20 minutes. A solution containing 0.004 moles of $NaNO_2$ dissolved in 10 mL of distilled water was gradually added to the mixture dropwise. Then, 0.004 moles of 4,5-diphenyl-1H-imidazole and 1 gm of sodium hydroxide were dissolved in 30 mL of distilled water that had been pre-cooled to a temperature between 0-5°C, and 5 mL of absolute ethanol were added gradually to each of the produced solutions. After observing the precipitation of an azole derivative, the solution was stirred continuously for an hour and then left for a whole day. The resulting precipitate was then filtered, washed with distilled water, dried thoroughly, and purified by recrystallization with absolute ethanol [21]. The percentage was 71.45%, and its melting point is 163-165°C. The reaction pathway for the synthesis of Azo derivative (A1) in Scheme (1).

**Synthesis of Schiff base derivative (S1) N-(2-((4,5-diphenyl-1H-imidazol-2-yl)diazenyl)benzyl)-1-(3-phenyl-1H-pyrazol-4-yl)methanimine**

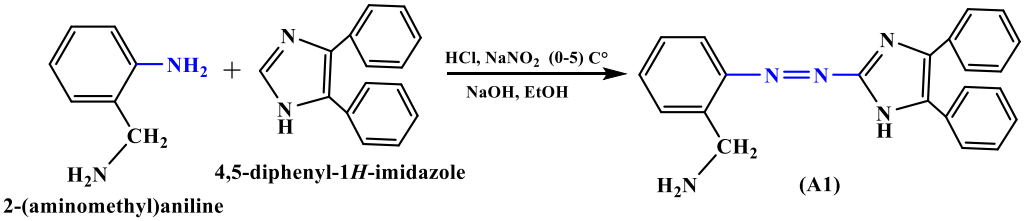
In a round-bottom flask, 0.0014 moles of the azo derivative prepared in the initial step was mixed with 0.0014 moles of 3-phenyl-1H-pyrazole-4-carbaldehyde in 30 mL of pure ethanol with two to three drops of glacial acetic acid present.

For 22 hours, the mixture was refluxed at 78°C, during which the reaction was monitored using TLC with a mobile phase of benzene and ethanol in a ratio of 1:4. At the end of the reaction, the mixture was filtered, dried, and recrystallized using pure ethanol [22]. The percentage was 61.38 %, Rf=0.69, and its melting point is 170-172°C. The reaction pathway for the synthesis of the Schiff base derivative (S1) is in Scheme (2).

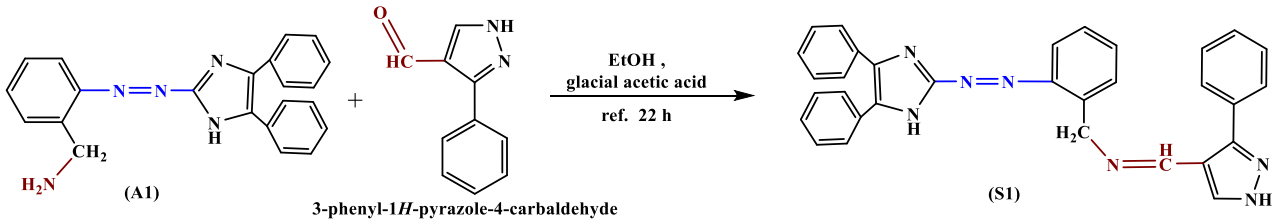
**Synthesis of β -Lactam derivative (B1) 3-chloro-1-(2-((4,5-diphenyl-1H-imidazol-2-yl)diazenyl)benzyl)-4-(3-phenyl-1H-pyrazol-4-yl)azetidin-2-one**

Mix 0.0009 moles of the derivative of the Schiff base (S1) with 0.0018 moles of triethylamine in 25 mL of 1,4-dioxane. Then add to this mixture, cooled to 10°C, 0.0009 moles of chloroacetyl chloride dropwise with continuous stirring for (39 hours).

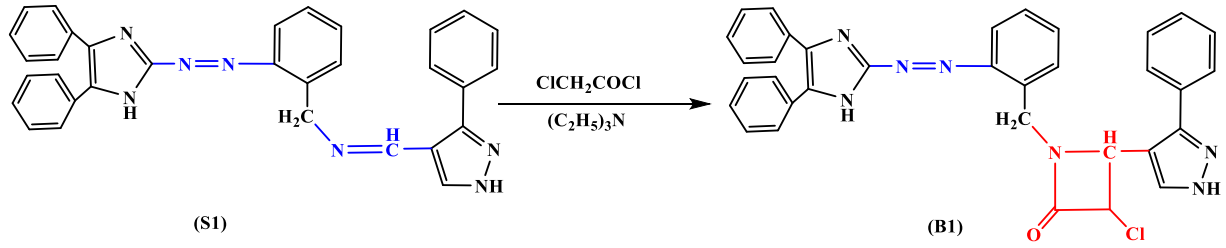
The reaction was monitored using TLC with a mobile phase of benzene and ethanol in a ratio of 1:4. At the end of the reaction, the mixture was filtered, dried, and recrystallized using pure ethanol. [23,24]. The percentage was 63.50 %, Rf=0.76, and its melting point is 179-181°C. The reaction pathway for the synthesis of β-Lactam derivative (B1) in Scheme (3).




**Scheme 1.** Synthesis of Azo derivative (A1).




**Scheme 2.** Synthesis of Schiff base derivative (S1).




**Scheme 3.** Synthesis of β -Lactam derivative (B1).

## 3. Results and Discussion

### 3.1. Azo derivative (A1)

FT-IR spectrum analysis revealed an absorption band at a wavenumber of 1450 $cm^{-1}$ for the stretching of the Azo group (N=N). The aromatic amine group ($-NH_2$) attached to the benzene ring is what participates in the formation of the azo group in this compound, as only aromatic amines are capable of forming stable diazonium salts, which is a prerequisite for azo reactions, and the absorption bands observed at 3353 and 3280 $cm^{-1}$ are attributed to the stretching vibrations of the amine group ($-NH_2$), 3398 $Cm^{-1}$for (-N-H), 3018 $Cm^{-1}$ for (-C-H)Aromatic. (2916,2898) $Cm^{-1}$ for (-C-H)Aliphatic, 1655 $cm^{-1}$ for (-N-H), (1605,1510) $cm^{-1}$ for (-C=C-)Aromatic, (1426 and 1367) $cm^{-1}$ for ($-CH_3$), 1294 $cm^{-1}$ for (-C=N) and 1249 $cm^{-1}$ for (-C-N). In the $^1$H-NMR spectrum, the azo derivative (A1) exhibited signals corresponding to : 12.04 (S,1H,N-H imidazole),7.86-7 (M,١٤H,Ar-H), 5.14 (S,2H,$NH_2$), 3.49 (S,2H,$-CH_2$). The $^{13}$C-NMR spectra of azo derivative (A1) showed the presence of: 147 for ($C_{2,3}$), 143 for ($C_5$), 136 for ($C_{20}$), 133-117 for ($C_{arom.}$), 46 for ($C_{26}$) (Fig. 1 supp.).

### 3.2. Schiff base derivative (S1)

FT-IR spectra data: disappearance of two absorption peaks at 3431 and 3324 $cm^{-1}$ for the stretching vibrations of amine group ($-NH_2$) (Fig. 2 supp.). Meanwhile, the appearance of a new peak at 1667 $cm^{-1}$ for an imine (-C=N) bond, while a signal at 3403 $cm^{-1}$ confirmed the presence of an N–H imidazole functional group, and the absorption bands observed at 3403 $cm^{-1}$ for (-N-H), 3060 $cm^{-1}$ for (-C-H) Aromatic. (2931,2859) $cm^{-1}$ for (-C-H)Aliphatic, (1602,1507) $cm^{-1}$ for (-C=C-)Aromatic, 1446 for (-N=N-), (1379 and 1276) $cm^{-1}$ for ($-CH_3$), 1244 $cm^{-1}$ for (-C=N) and 1156 $cm^{-1}$ for (-C-N). $^1$H-NMR spectrum, the Schiff base derivative (S1) exhibited signals corresponding to : 12.19 (S,1H,N-H imidazole), 11.67 (S,1H,N-H imidazole), 8.80 (S,1H,N=CH), 7.86-7.16 (M,19H,Ar-H), 3.49 (S,2H,$-CH_2$). The $^{13}$C-NMR spectra of Schiff base derivative (S1) showed the presence of: 165 for ($C_{28}$), 149 for ($C_{25,26}$), 144 for ($C_{23}$), 136 for ($C_8$), 133-117 for ($C_{arom.}$), 56 for ($C_2$) .

### 3.3. β-Lactam derivative (B1)

The FT-IR spectrum was showed the disappearance of the imine (N=C) absorption band at 1667 $cm^{-1}$, accompanied by the appearance of a new band at 1744 $cm^{-1}$, indicating the stretching vibration associated with the lactam carbonyl group (-C=O–N–), and the absorption bands observed at 3471 $cm^{-1}$for (-N-H), 3057 $cm^{-1}$ for (-C-H)Aromatic. (2932,2856) $cm^{-1}$ for (C-H)Aliphatic, (1595,1503) $cm^{-1}$ for (-C=C-)Aromatic, 1451 $cm^{-1}$ for (-N=N-), (1389 and 1276) $cm^{-1}$ for ($-CH_3$), 1207 $cm^{-1}$ for (-C=N) and 1159 $cm^{-1}$ for (-C-N). $^1$H-NMR spectrum, the β-Lactam derivative (B1) exhibited signals corresponding to: 12.43 (S,1H,N-H imidazole), 11.95 (S,1H,N-H imidazole),7.96-7.12 (M,19H,Ar-H), 5.15 (S,1H,-CH-Cl), 4.67 (S,1H,-CH-N), 4.27 (S,2H,$-CH_2$). The $^{13}$C-NMR spectra of β-Lactam derivative (B1) showed the presence of: 169 for ($C_{40}$), 149 for ($C_{25,26}$), 143 for ($C_{23}$), 136 for ($C_8$), 131-117 for ($C_{arom.}$), 62 for ($C_{41}$), 53 for ($C_{28}$), 42 for ($C_2$) (Fig. 3 supp.).

### 3.4. Molecular Docking

Potential therapeutic candidates can be found by using molecular docking, a potent technique for determining the binding affinity between a ligand and its matching protein target [25]. This procedure entails estimating the complex's affinity and forecasting interactions between the protein and ligand molecules. Among the benefits of computational molecular docking are its speedy and economical screening of possible inhibitors as well as its precision in anticipating and comprehending the

interactions between a particular chemical and its target protein [26,27]. Because of these factors, molecular docking can be used to help create novel medications and even find new therapeutic targets for medications that already exist. Researchers can screen a large number of compounds to find those with the highest binding affinity for the target protein—for which the protein data bank (http://www.rcsb.org) provides detailed three-dimensional X-ray crystallographic coordinates—by conducting these simulations on a computer rather than in a lab [28]. In order to investigate plausible binding interactions with proteins PDP: 3DKF and further evaluate anti-inflammatory properties, we were interested in employing computational molecular docking. While the proposed medicine molecule is considered flexible for binding to the receptor, the receptor protein must stay stiff [29].

### 3.5. Molecular Docking Study with the Protein Responsible for Breast Cancer MCF-7

Molecular docking was studied with the protein (PDP:3DKF) obtained from Protein Data Bank, where molecular docking was examined with the binding sites (Site1) as shown in the Table 1.

A study of the binding of compounds prepared with the target protein at the active site (Site 1) showed varying affinities between the compounds and the target protein or enzyme. After examining the active sites and the binding interactions with the amino acids of this protein, it was found that the interactions affect the basic amino acids and form hydrogen bonds and hydrophobic interactions inside the protein's active site. The β-Lactam derivative (B1) showed a correlation value of -8.78 and an RMSD value of (2.40). Table 2 illustrates the correlation values and hydrogen bonds of the prepared derivatives (Figure 1).

### 3.6. Study of Biological Activity on Cancer Cells

The MCF-7 breast cancer cell line and the normal WRL-68 cell line were compared in this study to show how well they worked on human body cells and how they may be employed as cancer medications. We'll go into great depth on how the β-Lactam derivative (B1) affects both healthy and cancerous cells [30]. All cells were biologically examined using the MTT test, and the findings indicated that the kind of produced derivative and its concentration have a substantial impact on the rate of cell inhibition [31]. The highest rate of inhibition for breast cancer cells and normal cells showed growth at a concentration of 400 µg/ml, which was the most effective inhibitory concentration when compared to other concentrations used in evaluating the impact of the synthesized derivative on the proliferation of MCF-7 breast cancer cells and normal WRL-68 cells [32]. According to the accompanying Table 3 and Figure 2, the β-Lactam derivative (B1) exhibited a half-maximal inhibitory concentration (IC50) of 102.2 µg/mL for killing half of the cancer cells and a lower impact on normal cells, needing 230.1 µg/mL to inhibit half of the normal cells.

**Table 1.** Molecular docking study with sites.

| Receptors | Sites | Residues |
|---|---|---|
| 3DKF | Sites 1 | (VAL1083 ILE1084 GLY1085 ARG1086 VAL1092 ALA1108 LYS1110 LEU1140 LEU1157 PRO1158 TYR1159 MET1160 GLY1163 ASP1164 ARG1166 ASN1167 ARG1170 ASP1204 ARG1208 ASN1209 MET1211 ALA1221 ASP1222 ALA1226 ASP1228 MET1229 TYR1230 NME1231 LYS1244 LEU1245 PRO1246 TRP1249 VAL1359 LYS1360 GLU1361 NME1362) |
| | Sites 2 | (ILE1169 ARG1170 ASN1171 GLU1172 MET1277 THR1278 ARG1279 GLY1280 ALA1281 PRO1282 PRO1305 GLU1306 TYR1307 VAL1350 HIS1351 VAL1352 ASN1353 TYR1356 VAL1357 ASN1358 VAL1359 LYS1360) |

**Table 2.** It explains the correlation values and hydrogen bonds of β-Lactam derivative (B1).

| Com. | S score (Kcal/mol) | RMSD (Ă) | Atom of compound | Atom of receptor | Involved Receptor residues | Type of Interaction bond | Distance (Ă) | E (Kcal/mol) |
|---|---|---|---|---|---|---|---|---|
| B1 | -8.78 | 2.40 | CL42<br>6-ring | OD1<br>6-ring | ASP1164<br>TYR1230 | H-donor<br>pi-pi | 3.13 | -5.6 |

**Table 3.** Evaluation of the impact of the β-Lactam derivative (B1) on MCF-7 breast cancer cells and its comparative analysis with the normal WRL-68 cell line.

| Concentration (µg mL$^{-1}$) | Mean viability (%) ± SD | |
|---|---|---|
| | WRL-68 | MCF-7 |
| 400 | 72.168±1.12 | 40.96±2.85 |
| 200 | 85.02±1.27 | 50.76±6.8 |
| 100 | 93.28±0.8 | 71.79±5.37 |
| 50 | 97.33±0.50 | 90.73±4.9 |
| 25 | 97.29±0.88 | 95.36±0.69 |

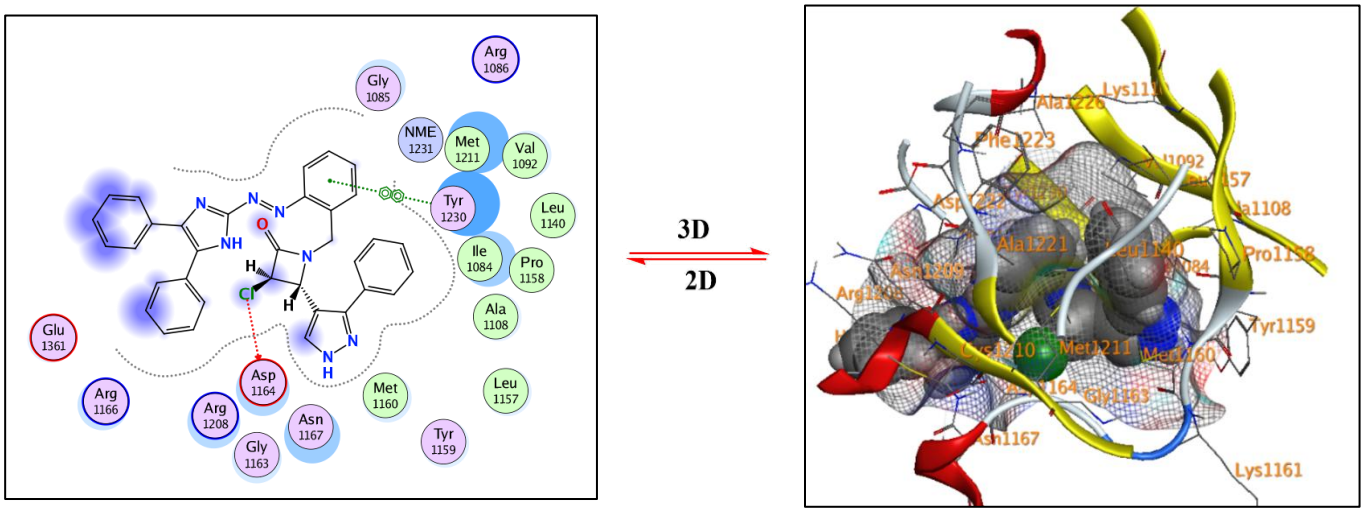



**Fig. 1.** Molecular modelling of β-Lactam derivative (B1)

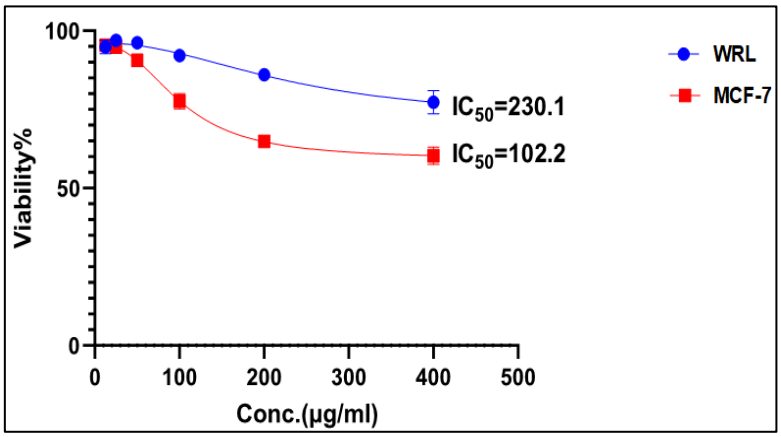



**Fig. 2.** The $IC_{50}$ of the β-Lactam derivative (B1) for inhibiting MCF-7 breast cancer cells and WRL-68 normal cells.

## 4. Conclusion

In this study, a novel β-Lactam derivative (B1) was successfully synthesized, and its structure was elucidated through comprehensive spectroscopic analyses comprising FT-IR, 1H-NMR, and 13C-NMR. The β-Lactam derivative exhibited remarkable biological activity, as molecular docking studies revealed a strong binding affinity of the β-Lactam derivative toward a breast cancer-associated target protein (MCF-7, Proteomic Database ID: 3DKF), suggesting its potential efficacy as a therapeutic agent. Additionally, in vitro cytotoxicity tests confirmed the selective antiproliferative effect of the compound, showing significant cytotoxicity against MCF-7 cancer cells while exerting negligible toxicity on normal WRL-68 cells. These results suggest that β-Lactam derivative is a candidate compound for the development of new therapeutic approaches for cancer. Further studies, including in vivo efficacy and pharmacokinetic studies, are needed to fully evaluate its clinical potential.

## Supplementary files

Supplementary file 1.

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