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DESIGN, GREENSYNTHESIS AND MOLECULAR DOCKING STUDIES OF A NOVEL 2,4,5-TRIPHENYL IMIDAZOLE DERIVATIVE

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Keywords:

2,4,5- Triphenyl imidazole, Acid chlorides, Green chemistry, Microwave assisted synthesis, Docking studies

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ABSTRACT: The design and synthesis of a novel 2,4,5- Triphenyl imidazole derivative has been achieved using a green chemistry approach. These compounds were synthesized by using a sustainable catalytic material and solvent free one-pot reaction where benzil, aromatic aldehydes, ammonium acetate and acid chloride were reacted under microwave irradiation. This method offers several advantages including simplicity, high yields, and short reaction times, making it more environmentally friendly and alternative to conventional methods. The synthesized compounds were characterized by determination of melting point, thin layer chromatography and Fourier transformer infrared spectra. Molecular docking studies were performed to evaluate the binding affinity of the derivative with the proteins 4XMB (Crystal structure of 2, 2'-(naphthalene-1, 4-diylbis (4-methoxyphenyl) sulfonyl) azanediyl) diacetamide bound to human Keap1 Kelch domain)) and 6BIV (HLA-DRB1 in complex with citrullinated LL37 peptide). The docking results indicated that the novel 2,4,5-triphenyl imidazole derivative has significant binding affinity with the protein 4XMB and showed poor binding affinity with the protein 6BIV.

INTRODUCTION: In the domains of chemistry, the synthesis of bioactive heterocyclic compounds like imidazole derivatives has attracted a lot of attention because of their many biological activities, which include antifungal, antibacterial, anticancer, and anti-inflammatory qualities [1]. Because of their exceptional pharmacological characteristics, triphenyl imidazole derivatives stand out among the others [2]. However, the use of ecologically hazardous solvents and reagents, severe temperatures, and extended reaction times in traditional synthesis poses significant challenges in terms of sustainability and efficiency [3-5].

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The development of more environmentally friendly and sustainable synthetic techniques has been fueled in recent years by the concepts of green chemistry. By using fewer hazardous substances and using less energy, green synthesis seeks to lessen the negative effects of chemical processes on the environment. With benefits including shorter reaction times, higher yields, and the capacity to work in softer environments, microwave-assisted synthesis has become a potent method in this area. Because it may speed up chemical processes and provide homogeneous heating, the use of microwave irradiation in organic synthesis is particularly promising [6, 7].

One-pot synthesis is a technique that allows many sequential reactions to occur in a single reaction vessel without the need for intermediary workups, thus improving the efficiency and simplicity of chemical processes. This method lowers trash production and solvent use overall while also

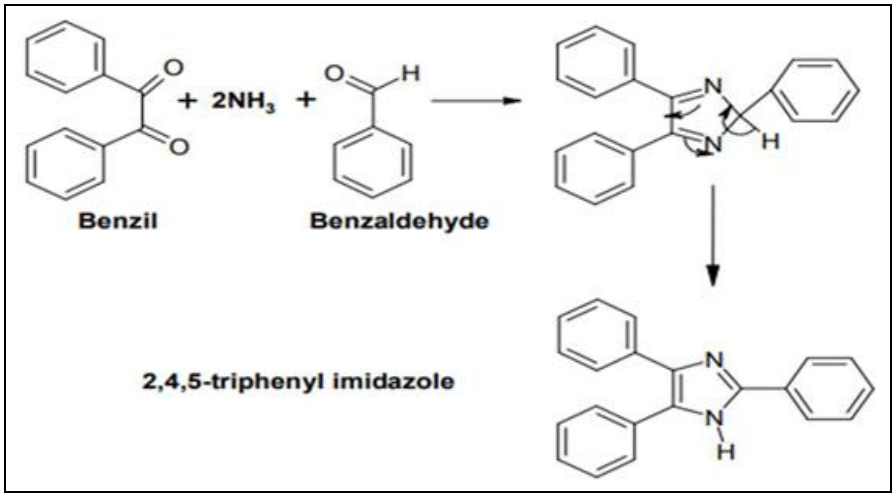
streamlining the synthetic process. A more potent technique for the quick and long-term synthesis of complex compounds is one-pot synthesis in conjunction with microwave irradiation [8, 9].

Acid chlorides, amines, and aldehydes condense to produce derivatives of triphenyl imidazole. Because acid chlorides are very reactive and may help create a variety of functional groups, they are useful reagents in organic synthesis. The synthesis of triphenyl imidazole derivatives from acid chlorides using microwave-assisted one-pot synthesis is a novel technique that adheres to the concepts of green chemistry and provides a sustainable substitute for conventional techniques. By using molecular docking, one may infer information about a tiny molecule's possible biological activity by predicting its preferred orientation when it binds to a target protein. This method makes it easier to identify and optimize lead molecules, which is essential for drug discovery and development. Biologically active and selective molecules can be designed and synthesized by integrating molecular docking studies with experimental synthesis [10-12].

The aim of the study was to employ microwave-assisted techniques for the efficient and sustainable synthesis of triphenyl imidazole derivatives and to utilize molecular docking studies to assess and optimize their potential biological activities. The objective of this study is to develop a green synthetic route for the preparation of triphenyl imidazole derivatives using microwave-assisted one-pot synthesis with acid chlorides and to evaluate their potential biological activity through molecular docking studies. This approach not only aims to provide an efficient and sustainable method for synthesizing these compounds but also to explore their interactions with biological targets, thereby contributing to the development of new therapeutic agents.

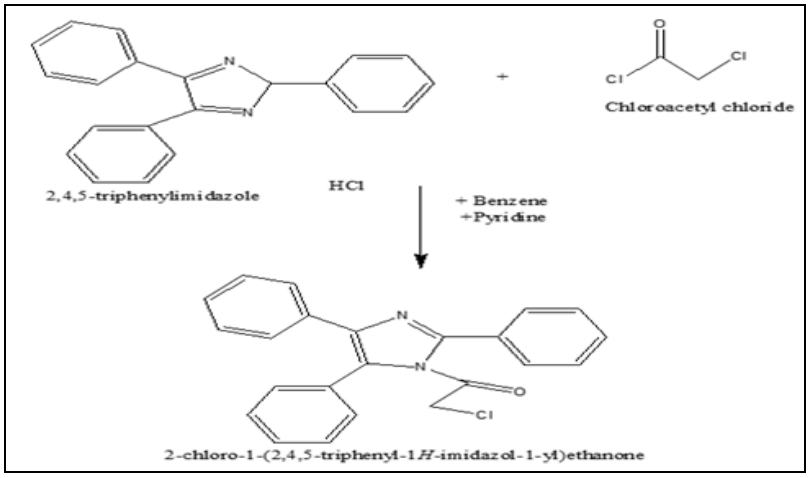
MATERIALS AND METHODS: Microwave oven, Electro thermal melting apparatus, TLC plates, UV chamber, Bruker Alpha-2 FT-IR instrument, Chemdraw ultra 8.0 version (2D) & 12.0 version (3D), Auto dock tools 1.5.7 version, Auto dock vina, Biovia Discovery studio 2021, Dwimperl, MGL tools were used for the study. Chemicals used are pharmacopeial or Analytical grade.

Synthesis of 2,4,5 Triphenyl-1H-imidazole [8, 9]: 2 gm of benzil, 2 gm of ammonium acetate, 4 ml of benzaldehyde and 4 ml of glacial acetic acid were taken in a flask and homogenized for uniform mixing. The reaction mixture was set for microwave assisted synthesis at a temperature of 100°C for a period of 20 minutes. TLC was performed for checking the completion of the reaction. Then it was filtered, allowed to stand to attain room temperature and neutralized with ammonium hydroxide. The resulting filtrate was then dried and recrystallized using ethanol.



Synthesis of 2,4,5 Triphenyl-imidazole Derivative (2-chloro-1-(2, 4, 5-triphenyl-1-H-imidazol-1-yl) Ethanone): 2.3 g of 2,4,5-Triphenyl-imidazole and 3.18 mL of chloroacetyl chloride were taken into a flask and 0.5 ml of benzene and 0.5 ml of pyridine were added. And

the reaction mixture was homogenized and set for microwave assisted synthesis at a temperature of 80°C for a period of 20 minutes. TLC was performed for checking the completion of the reaction. The product was allowed to stand to attain room temperature and neutralized with ammonium hydroxide. Then it was filtered and the obtained filtrate was dried & recrystallized with ethanol to obtain 2-chloro-1-(2,4,5-triphenyl-1-H- imidazol-1-yl) ethanone.



RESULTAND DISCUSSION: The obtained 2-chloro-1-(2, 4, 5-triphenyl-1-H- imidazol-1-yl) ethanone was synthesized using simple reaction conditions and easily available reagents. The compound was purified by recrystallization and obtained good yield. The purity of the product was checked by recording their melting points, yields and Rf values from the thin layer chromatography. **Table 1** shows the melting point and yield of 2, 4, 5-triphenyl imidazole and 2-chloro-1-(2,4,5-triphenyl-1-H- imidazol-1-yl) ethanone. Chromatography is an essential technique for identifying the synthesis of novel compounds and assessing their purity. Each compound has a characteristic Rf value. The solvent system for the chromatogram development was made by combining hexane and ethyl acetate (9:1). The plates were developed using an ascending approach, once the solvent front had travelled 8–10 cm, then the plates were removed and allowed to dry at the room temperature. The UV Chamber was used to identify the developed spots.

The formula was used to get the compounds' Rf values.

Rf = (Distance travelled by sample) / (Distance travelled by solvent front)

It was discovered that the Rf value of the obtained derivative was different from the parent and intermediate compounds, proving that the compound produced was completely distinct. Since, every sample produced a single spot, it was assumed that the compounds were impurity-free. The compounds' Rf values were shown in the **Table 2** and **3.** They show the Rf values of Benzil *vs*. 2,4,5 triphenyl imidazole (intermediate) and 2,4,5 triphenyl imidazole (intermediate) vs derivative.

The structure of the compound was characterised by recording the FTIR spectra which is shown in **Fig. 2** and spectral data is shown in **Table 4.**

The derivative was docked at the PDB code 4XMB and 6BIV to predict the best possible binding modes which is shown in **Table 5** and **6** respectively. And their docked view was shown in **Fig. 3** and **4.**

TABLE 1: PHYSICAL DATA

Compound	Molecular formula	Solubility	Appearance	Odour	M.Wt (g/mole)	Melting point	% yield
Triphenyl imidazole	C21H16N2	Acetone	Yellow crystals	Fruity	296.37	274° C	82.14%
Derivative (2-chloro-1-(2,4,5-triphenyl-1H-imidazole-1-yl) ethenone)	C23H17N2OCl	Acetone	Brown crystals	Pungent	372.5	204°C	76.12%

TABLE 2: RF VALUES OF BENZIL *VS.* 2,4,5 TRIPHENYL IMIDAZOLE (INTERMEDIATE)

Compound	Rf value (Hexane: Ethyl acetate) (9: 1)
Benzil	0.76
Intermediate (2,4,5-Triphenyl-imidazole)	0.88

TABLE 3: RF VALUES OF 2,4,5 TRIPHENYL IMIDAZOLE (INTERMEDIATE) *VS* DERIVATIVE

Compound	Rf value (Hexane: Ethyl acetate) (9: 1)
Intermediate(2,4,5-Triphenyl-imidazole)	0.88
Derivative (2-chloro-1-(2,4,5-triphenyl-1H-imidazole-1-yl) ethenone)	0.68

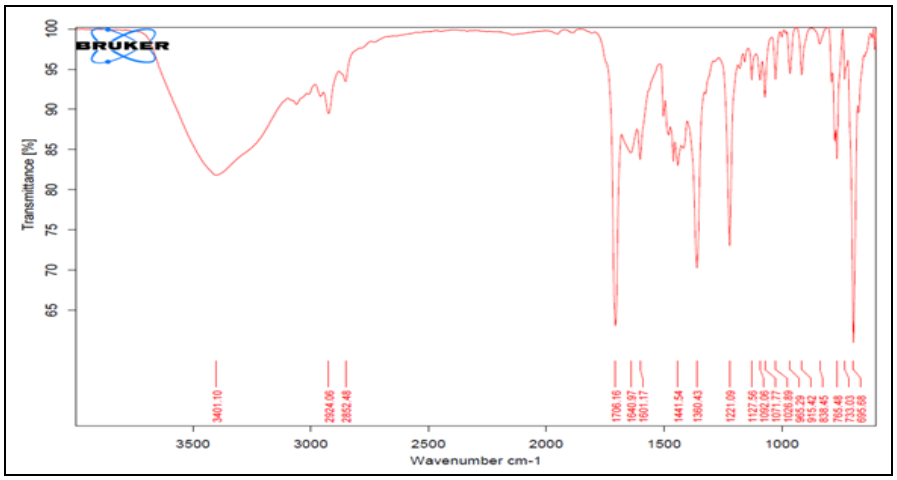


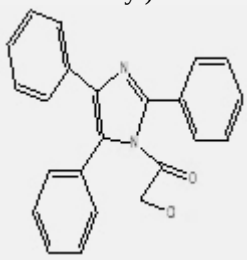
FIG. 1: FTIR SPECTRA OF THE SYNTHESIZED 2-CHLORO-1-(2,4,5-TRIPHENYL-1H-IMIDAZOLE-1-YL) ETHENONE

Based on IR spectrum, a broad peak at 3401 cm^{-1} indicates N-H Imidazole ring stretching, sharp peak at 3123 cm^{-1} indicates C-H aromatic Stretching, strong peak at 1706.1 cm^{-1} indicates C=O ketone group stretching, sharp peak at 1601.7 cm^{-1} indicates C=N Imidazole ring stretching, in addition, this is also supported by the peaks in the area of 838.45 7 cm^{-1} which is out of plane vibration of the aromatic ring.

TABLE 4: FTIR SPECTRAL DATA FOR 2-CHLORO-1-(2, 4, 5-TRIPHENYL - 1H - IMIDAZOLE-1-YL) ETHENONE

Wave number (1/cm)	Functional groups
3401	N-H (Imidazole ring) stretching
3123	C-H (Aromatic) Stretching
1706.1	C=O (Ketone group) stretching
1640	C=C (Aromatic) stretching
1601.7	C=N (Imidazole) stretching
838.45	C-Cl Stretching
695	C-H bending in aromatic ring

TABLE 5: DOCKING SCORES AND RESIDUE INTERACTIONS OF 2-CHLORO-1-(2,4,5-TRIPHENYL-1H-IMIDAZOLE-1-YL) ETHENONE WITH 4XMB

Code and structure of receptor	Structure of ligand	Ligand orientation positions	Score	Residual interaction
4XMB Crystal structure of 2,2'-(naphthalene-1,4-diylbis(((4-methoxyphenyl) sulfonyl) azanediyl))diacetamide bound to human Keap1 Kelch domain 	2-chloro-1-(2,4,5-triphenyl-1H-imidazole-1-yl) ethenone 	Ligand-1 Ligand-2 Ligand-3 Ligand -4 Ligand-5 Ligand-6 Ligand -7 Ligand-8 Ligand-9	-9.2 -8.8 -8.8 -8.7 -8.6 -8.6 -8.5 -8.5 -8.5	Conventional hydrogen bond with pi-pi -420, pi-pi T shape 485 stacked, bump of the bond-178, positive-positive charges value 4.81, pi-alkyl 4.81

Inference –2-chloro-1-(2,4,5-triphenyl-1H-imidazole-1-yl) ethenone has good binding interaction with Keap1 (4XMB) which is indicated by a docking score above -9. Which implies that the compound has the potential to modulate the Nrf2 pathway, thereby suggesting a strategy for treating diseases associated with oxidative stress and inflammation

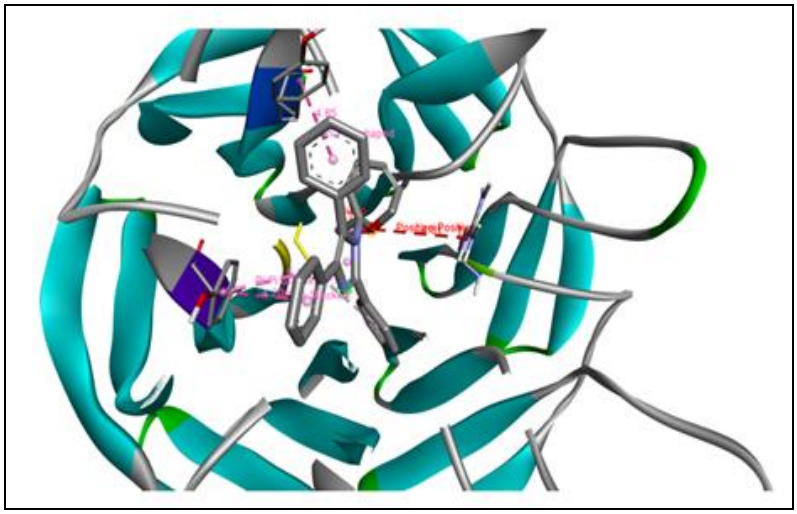


FIG. 2: 3D STRUCTURE OF 2-CHLORO-1-(2,4,5-TRIPHENYL-1H-IMIDAZOLE-1-YL) ETHENONE FOR BINDING INTERATIONS WITH 4XMB RECEPTOR

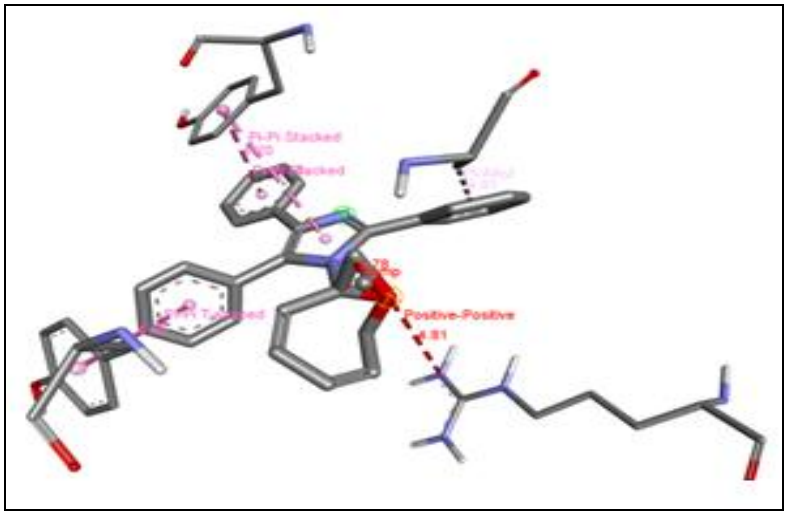


FIG. 3: 3D STRUCTURE OF 2-CHLORO-1-(2,4,5-TRIPHENYL-1H-IMIDAZOLE-1-YL) ETHENONE WITH 4XMB RECEPTOR IN RIBBON MODEL

TABLE 6: DOCKING SCORES AND RESIDUE INTERACTIONS OF 2-CHLORO-1-(2,4,5-TRIPHENYL-1H-IMIDAZOLE-1-YL) ETHENONEWITH 6BIV

Code and structure of receptor	Structure of ligand	Ligand orientation positions	Score	Residual interaction
6BIV HLA-DRB1 in complex with citrullinated LL37 peptide	2-chloro-1-(2,4,5-triphenyl-1H-imidazole-1-yl) ethenone	Ligand-1 Ligand-2 Ligand-3 Ligand -4 Ligand-5 Ligand-6 Ligand -7 Ligand-8 Ligand-9	-4.8 -4.0 -3.7 -3.7 -3.6 -3.6 -3.6 -3.6 -3	Amide-pi stacked asp b: 27 Vanderwals, gly b:28 Pi-anion glu b:141, asp b:25 Pi-alkyl val b:6 Ile b:8

Inference – A docking score below -9 indicate that 2-chloro-1-(2,4,5-triphenyl-1H-imidazole-1-yl) ethenone has poor binding interaction with HLA-DRB1 complex with the citrullinated LL37 peptide (6BIV). Which suggests that the compound does not effectively interact with this MHC class II-peptide complex so the compound is unlikely to influence immune processes involving this specific complex.

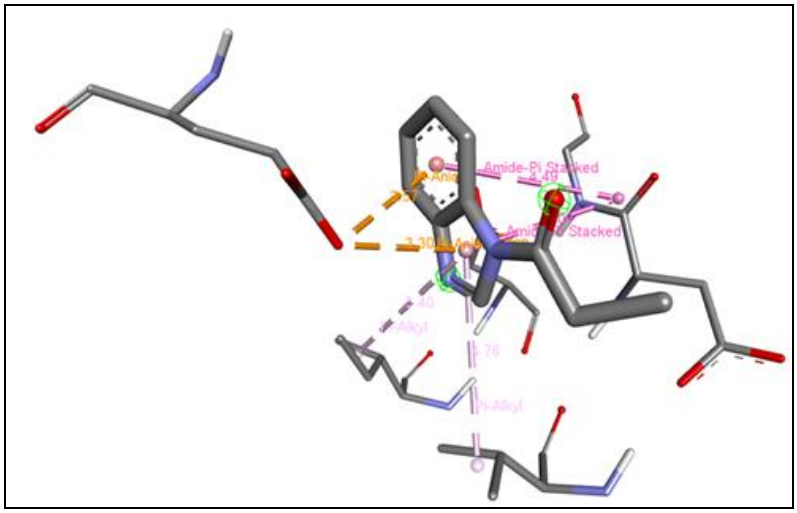


FIG. 4: 3D STRUCTURE OF 2-CHLORO-1-(2,4,5-TRIPHENYL-1H-IMIDAZOLE-1-YL) ETHENONE FOR BINDING INTERATIONS WITH 6BIV RECEPTOR

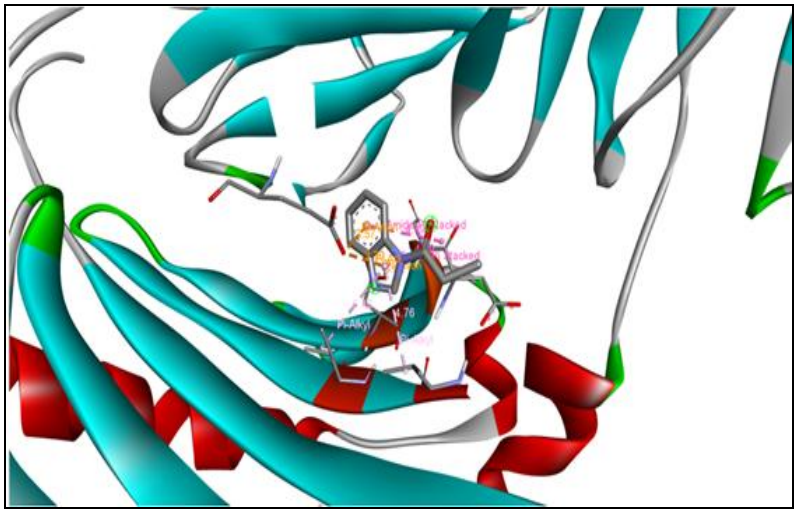


FIG. 5: 3D STRUCTURE OF 2-CHLORO-1-(2,4,5-TRIPHENYL-1H-IMIDAZOLE-1-YL) ETHENONE WITH 6BIV RECEPTOR IN RIBBON MODEL

CONCLUSION: A green synthetic route for the preparation of a novel triphenyl imidazole derivative, 2-chloro-1-(2, 4, 5-triphenyl-1H-imidazole-1-yl) ethenone using microwave-assisted one-pot synthesis with acid chlorides was prepared as per the proposed scheme. The synthesized compounds were characterized by various physico-chemical parameters and by spectral studies, which includes solubility, physical state, colour, odour, melting point, thin layer chromatography and FTIR. 2-chloro-1-(2,4,5-triphenyl-1-H- imidazol-1-yl) ethanoneis soluble in acetone, physical state is crystalline, brown colour, odour pungent, melting point found at 204°C, Rf value is found at 0.68 and percentage yield is 76.12%. A strong peak in a 1706.1 region due to the C=O stretch and a peak at 838.45 due to the C-Cl stretch confirms its formation. The docking studies revealed that 2-chloro-1-(2, 4, 5 - triphenyl - 1H – imidazole - 1 - yl) ethenone showed good binding affinity with Keap 1 (4XMB) which indicates it effectively modulates the Nrf2 pathway whereas it showed poor binding affinity with HLD-DRB1 complex (6BIV) which indicates that it does not show any influence on immune response involving the specific complex. Thus 2-chloro-1-(2,4,5-triphenyl-1H-imidazole-1-yl) ethenone can be developed into a therapeutic agent for conditions related to oxidative stress and inflammation, while being less relevant for autoimmune conditions involving the HLA-DRB 1-citrullinated peptide complex. While the findings are promising further investigation is necessary to confirm and fully understand the activity.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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