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Design, synthesis, *in silico* study, and anti-psoriatic activity of some novel Fumaric acid ester derivatives

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Psoriasis, being a chronic inflammatory and autoimmune disease, remains untreatable despite meticulous management and treatment therapies developed by scientists globally. Earlier, Fumaric acid ester derivatives were employed in clinical and preclinical settings to observe the benefits in psoriasis treatment. In the current study, some novel derivatives were designed, synthesized, formulated, and tested in the mouse tail model of psoriasis. The designed molecules were also docked on P38α-MAPK enzyme, which is believed to play an important role in generating cytokines and further other mediators responsible for psoriasis. Molecular docking was performed using Schrodinger 2024-1. Results indicated that out of fourteen designed compounds, three compounds (compounds 2 (2E)-4-(octyloxy)-4-oxobut-2-enoic acid, Compound 3 (2E)-4-(diphenylmethoxy)-4-oxobut-2-enoic acid and Compound 4 (2E)-4-(cyclopentoxy)-4-oxobut-2-enoic acid) were properly synthesized and characterized and confirmed by spectroscopic techniques and then were subjected to be evaluated pharmacologically in mouse tail model. Among them, compound 2 exhibited the highest binding energy (-1.908 kcal/mol) and convincing binding interactions and can be considered for the inhibition of the enzyme. Molecular docking results were in agreement with the *in vivo* study, indicating the presence of orthokeratosis and alleviating other cardinal signs of psoriasis in the mouse tail.

Keywords: Erythematous plaques, Fumaric acid ester (FAE), Mitogen-activated protein kinase, Mouse tail model, Orthokeratosis, Psoriasis, Synthesis

Psoriasis is a chronic, immune-mediated skin disease characterised by the presence of erythematous plaques with silvery scaling, typically affecting the extensor surfaces and the scalp. It is associated with significant morbidity, psychological stress, and impaired quality of life[1]. The pathogenesis of psoriasis is multifactorial, involving genetic predisposition, immune dysregulation, and environmental triggers[2]. A hallmark feature of psoriatic skin is the hyperproliferation and aberrant differentiation of keratinocytes, which occurs due to a shortened epidermal cell cycle and an influx of inflammatory cells. Recent research has identified immune-mediated pathways, particularly those involving the Th1 and Th17 cell subsets, as central to the disease mechanism. The role of human leukocyte antigen (HLA) Cw6 and the effectiveness of immunosuppressive agents like cyclosporine further support the immune-driven nature of psoriasis[3-5]. Various clinical manifestations exist, ranging from plaque and guttate psoriasis to more severe forms such as erythrodermic and pustular psoriasis, often accompanied by psoriatic arthritis. Despite a broad spectrum of available therapies—including topical corticosteroids, vitamin D analogues, phototherapy, and systemic agents such as methotrexate, cyclosporine, and biologics—long-term management remains a challenge due to adverse effects, cost, and reduced efficacy over time[6,7].

Fumaric Acid Esters (FAEs) have emerged as promising agents in the management of moderate to severe psoriasis due to their immunomodulatory and anti-inflammatory effects. Initially proposed by Schweckendiek in 1959, the therapeutic potential of FAEs was attributed to their role in the citric acid cycle and modulation of oxidative stress pathways[8-10]. The esterification of fumaric acid enhances its bioavailability while reducing gastrointestinal irritation, a limitation of the parent compound. Among various esters, dimethyl fumarate (DMF) and monomethyl fumarate (MMF) have shown the most

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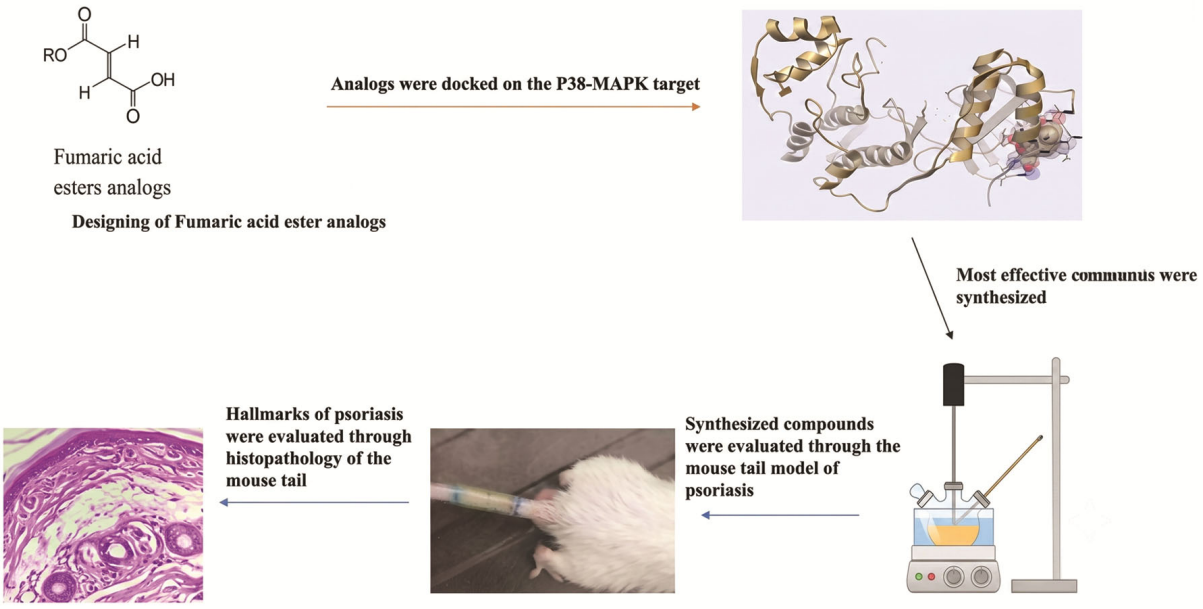

Graphical abstract

potent biological activity, primarily through activation of the Nrf2 pathway and suppression of pro-inflammatory cytokines such as IL-17 and TNF-α[11,12].

The synthesis of novel fumaric acid analogues presents an opportunity to optimise pharmacokinetics and minimise side effects associated with existing formulations. Structure-activity relationship (SAR) studies reveal that variations in alkyl chain length and branching can significantly influence the potency, stability, and immune-modulatory profile of FAEs[13]. Advances in green chemistry and enzymatic synthesis have further improved the feasibility of producing diverse FAE analogues with potential therapeutic applications[14,15]. Given the rising interest in alternative and sustainable therapies for psoriasis, this study focuses on the synthesis of novel fumaric acid ester analogues and their anti-psoriatic evaluation using experimental models and computational (*in silico*) tools. The overarching aim is to identify new candidates with enhanced efficacy, improved bioavailability, and better safety profiles for long-term management of psoriasis.

Materials and Methods

Chemicals

The reagents used in this study, including maleic anhydride, various alcohols, solvents, and analytical-grade chemicals, were procured from CDH and SD Fine Chemicals, Mumbai. Clobetasol was obtained from Canixa Life Sciences Pvt. Ltd.

Computational study

The 2D chemical structures of three fumaric acid ester analogues were drawn using ChemSketch 2015 (Freeware), and subsequently converted to 3D structures for molecular docking purposes. Further, Ligand preparation involved converting 3D-optimised.mol structures to .smi format using Open Babel 3.1.2. Protein target, i.e. p38α Mitogen-Activated Protein Kinase (PDB ID: 3LHJ) was retrieved from the RCSB Protein Data Bank. Protein and ligands were further prepared using protein preparation, and Ligprep Wizards of Schrodinger (2024-1) and finally docking was performed using Maestro 13.9 (Schrodinger 2024-1) [16,17]. During Ligand preparation, some conformers of the synthesised ligands were generated, which were segregated on the basis of energy level, and conformers with minimised energy were taken into consideration for docking purposes.

Synthesis of Analogues

Two general synthetic schemes were employed for the synthesis of fumaric acid ester analogues (Figs. 1 & 2).

This method involved the direct reaction of maleic anhydride with R-alcohols in the presence of iodine and toluene at ~155°C. The reaction mixture was hot-filtered, and the resulting compounds were recrystallised using light petroleum ether (Fig. 3)[18].

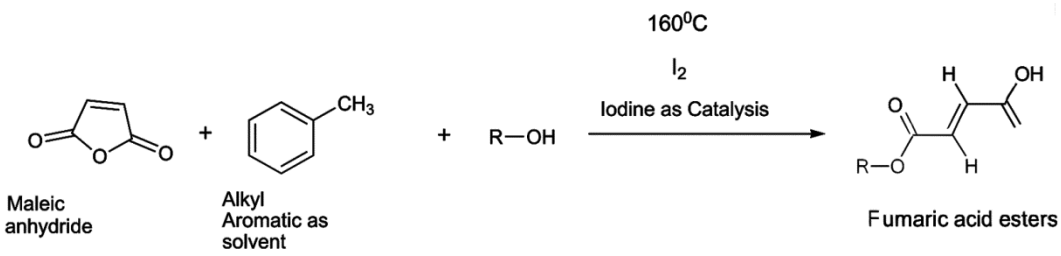

Fig. 1 — Direct Esterification of Maleic Anhydride of the synthesis of analogues of Fumaric acid ester

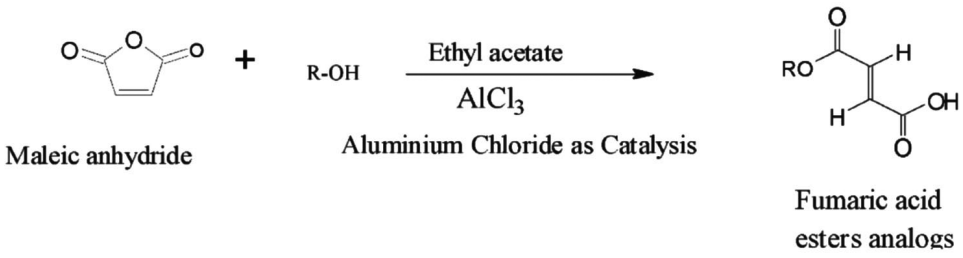

Fig. 2 — Monomethyl Fumarate Synthesis of the synthesis of analogues of Fumaric acid ester

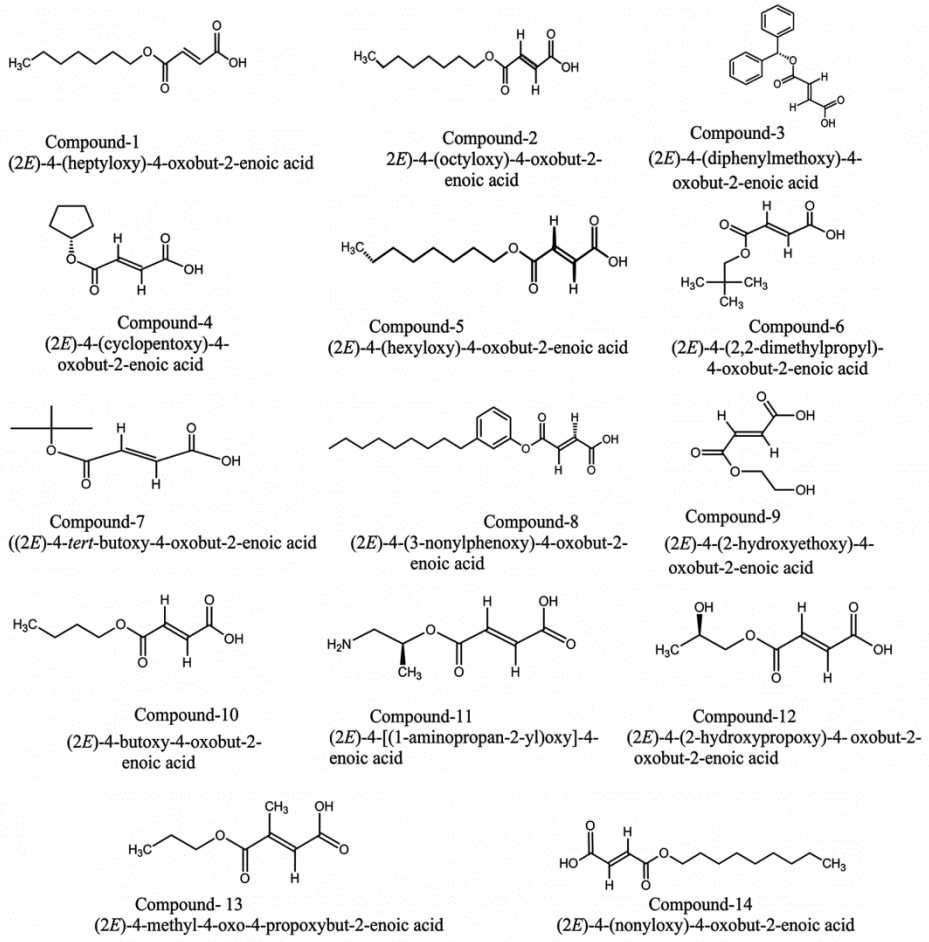

Fig. 3 — Newly designed analogues of Fumaric acid esters

Based on the method described by Dymicky *et al*.[19], maleic anhydride was reacted with substituted aromatic alcohols using aluminium chloride as a catalyst in ethyl acetate at 70–75°C. Products were filtered, washed, and recrystallised. The physical constants, such as melting and boiling points, were determined using open capillary and Thiele's tube methods. FTIR spectra were recorded using a Bruker Alpha spectrophotometer. Samples were scanned across 4000–400 cm^{-1} to identify characteristic functional groups.

Spectrographic analysis

TLC was performed using pre-coated silica gel G plates. The mobile phase used was a mixture of ethyl acetate, hexane, and chloroform in a 3:2:1 ratio. Spots were visualized under iodine vapor and Rf values were calculated[20]. Solubility profiles of synthesized compounds were tested in solvents including water, ethanol, methanol, acetone, DMSO, diethyl ether, and chloroform[21]. Presence of ester functionality was confirmed by a colorimetric reaction involving ethanol, NaOH, and phenolphthalein, indicated by a pink coloration. pH was estimated using pH indicator paper and compared against a colorimetric chart. NMR analyses were carried out on a Bruker Avance III 400 MHz spectrometer. Samples were dissolved in $CDCl_3$ (Deuterated chloroform) or DMSO-d_6 (Dimethyl sulphoxide- d_6), and TMS (Tetramethyl silane) was used as the internal standard. Mass spectra were obtained using High-Resolution Time-of-Flight Mass Spectrometry (TOF-MS) to determine molecular weights and confirm molecular formulas.

Formulation study

Carbopol 934 was dissolved in 60 mL of demineralized water over the course of 1 h with stirring to prevent clumping. Next, disodium edetate and triethanolamine were individually dissolved in 10 mL of demineralized water and stirred for 10 min. Stirred 4.83 mL of propylene glycol together with 12 mL of demineralized water for 10 min. A mixture of disodium edetate, triethanolamine, and Carbopol solution was stirred for 10 min until reaching a pH of 7.4 (Table 1). Next, the solution of propylene glycol was mixed in for 10 min while stirring until a uniform gel base formed[22].

Table 1 — Composition of Ligand gel base

Composition	Quantity in gm	Use of ingredients
Drug	1.5 g	For Anti-psoriatic Activity
Carbopol 934	1.5 g	Gelling agent
Triethanolamine	1.5 g	Moisturizing agent & Neutralizing agent
Disodium EDTA	0.005 g	Preservative
Propylene glycol	5 g	Humectant
Water	100g q.s.	Solvent

Evaluation of gel

pH: The pH of various gel formulations was determined by using a digital pH meter.

Spreadability: It was measured by the wooden block and glass slide apparatus. Approximately 20g of weights were placed into the pan, and the time started until the upper slide (movable) detached fully from the fixed slides. Spreadability was then calculated by using the formula:

$S = M.L / T$

Where, S = Spreadability

M = Weight tide to upper slide

L = Length of glass slide

T = Time taken to separate the slides from each other

Viscosity: The Brookfield viscometer was used to measure viscosity. A Brookfield viscometer (Model RVTDV II, Brookfield) was used to evaluate viscosity at room temperature (25–27°C).

Homogeneity: After the gel had set in the container, the developed gel was tested using a visual method to ascertain homogeneity. Their appearance was tested, and the existence of any aggregates was checked[23].

***In vivo* experimental study**

All animal experiments were conducted in accordance with CCSEA guidelines and were approved by the Institutional Animal Ethics Committee (IAEC) of Ram-Eesh Institute of Vocational and Technical Education, Greater Noida (Certificate No: RIT/IAEC/PG/2023-04).

Acute dermal toxicity

The acute dermal toxicity of synthesised analogues was assessed following OECD Guideline 402 [24,25]. Female Albino Wistar rats (200–250 g, aged 5–6 weeks) were used for the study. The dorsal fur (10% body surface area) was shaved before test substance application. Three dose levels (50 mg/kg, 300 mg/kg, and 1000 mg/kg) of test compounds were applied. Each group contained 3 rats. The test compounds were applied to the exposed area and covered with a porous gauze dressing secured with non-irritating tape (Table 2). Observations were

recorded at regular intervals (1, 24, 48, 72 hs and daily for 14 days) for behavioural changes, fur condition, systemic toxicity, and mortality. On day 14, animals were sacrificed via CO_2 inhalation. Organs were collected for gross pathology and organ index calculation:

Organ Index = (Organ weight (g) / Body weight (g)) × 100

Anti-psoriatic activity: Mice tail model

The mouse tail model was used to evaluate the anti-psoriatic efficacy of synthesised fumaric acid esters, as it closely mimics human epidermal characteristics[26]. Key pathological features such as parakeratosis, orthokeratosis, rete ridges elongation, and micro-abscesses were assessed histologically[27,28]. 48 male Swiss albino mice (20–30 g, aged 7–8 weeks) were divided into 8 groups (n=6). A 0.5 cm segment near the tail base was exposed, and the test formulation was applied topically. A plastic cylinder was fixed over the area for 2 hs and then removed. Applications were performed once daily, five times a week, for two weeks. Mice were sacrificed 2 hs after the final dose, and tail samples were collected for histological evaluation (Table 3).

Table 2 — Groups for Acute dermal toxicity (OECD Guideline 402)

S. No.	Group	Animals
1.	Control	3
2	Compound 2	
	50 mg/kg	3
	300 mg/kg	3
	1000 mg/kg	3
3	Compound 3	
	50 mg/kg	3
	300 mg/kg	3
	1000 mg/kg	3
4	Compound 4	
	50 mg/kg	3
	300 mg/kg	3
	1000 mg/kg	3

Table 3 — Groups for Mouse tail model of psoriasis

Group	Treatment	No. of Animals
I	Negative control	06
II	Clobetasol (Positive control)	06
III	Compound 1 (50 mg/kg)	06
IV	Compound 1 (100 mg/kg)	06
V	Compound 2 (50 mg/kg)	06
VI	Compound 2 (100 mg/kg)	06
VII	Compound 3 (50 mg/kg)	06
VIII	Compound 3 (100 mg/kg)	06

Results and Discussion

Molecular docking study

Molecular docking study indicated that all synthetic compounds docked in the active site of P38α-MAPK enzyme, and compound 2 exhibited more binding energy and quite similar binding pattern (Fig. 4, and Table 4).

Characterization of Ligand

Out of the designed fourteen ligands, only three ligands (Compound 2, 3, and 4) could be prepared by direct reaction of maleic anhydride with R-alcohols in the presence of iodine and toluene and the maleic anhydride was reacted with substituted aromatic alcohols using aluminium chloride as a catalyst in ethyl acetate. To optimize the reaction condition Heptanol, n-Octanol, Diphenyl carbinol, cyclopentanol, Hexanol, Neopentyl alcohol and Ethylene glycol were used as reacting agents to get the highest yield, which was upto 88% with a shorter reaction time. The ligands were characterised by various spectroscopic techniques like UV-Visible, FT-IR and NMR Spectroscopy (Figs. 5-10). Other ligands could not be processed further as the yield was very insignificant, hence they could not be characterised.

All synthesised ligands are stable and colourless compounds. These Complexes were prepared in very good yields (69.4%-88%). All are soluble in Acetone, Chloroform, DMSO and partly soluble in Ethyl acetate and insoluble in Water (Table 5).

FT-IR spectra of the ligands show peaks in the range of 1712-1725 cm^- assigned to (C=O) and 1559-1151 cm^- due to the presence of the ester group.

The Singlet peak is due to the presence of alkene group in 1H NMR spectra of Fumaric esters ligands.

Formulation study

The stability study did not show any substantial variations in pH, viscosity, spread ability, or homogeneity, which means that the formulation was able to maintain physical stability under the conditions tested (25 ± 2°C / 60 ± 5% RH and 40 ± 2°C / 75 ± 5% RH, over a period of 3 months) (Table 6).

Table 4 — Binding energy and interactions of ligands

S. No	Ligand	Binding Energy kcal/mol	Hydrogen bond interactions
1	Compound 2	-1.908	Lys53 (2.51Å), Asp168 (1.94Å)
2	Compound 3	-0.607	Ala34 (2.40Å), Lys53 (2.04Å), Asp168 (1.91Å)
3	Compound 4	-0.375	Asp168 (1.89Å)

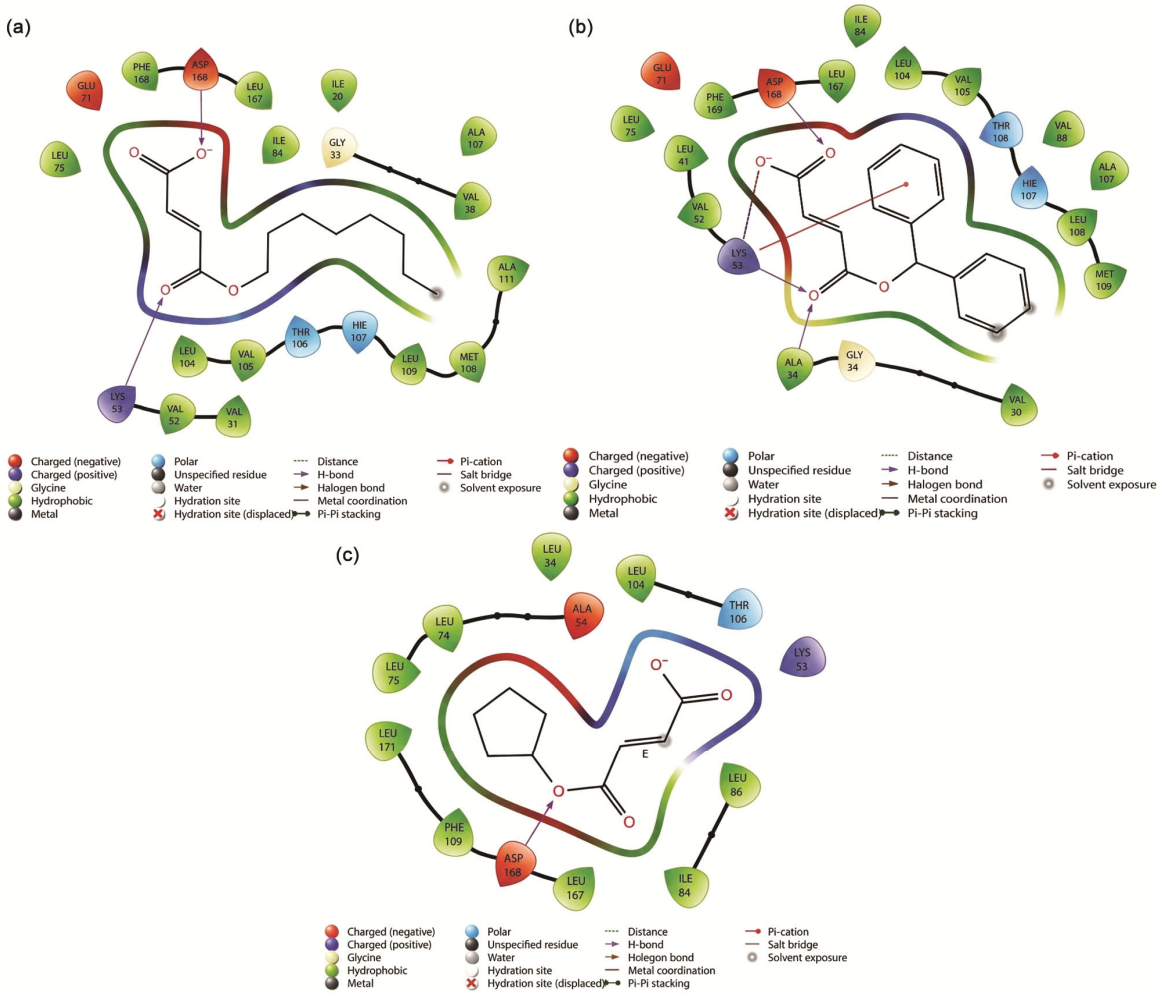

Fig. 4 — Demonstration of Binding Pattern of Ligands with P38α-MAPK enzyme (a) Compound 2; (b) Compound 3; and (c) Compound 4

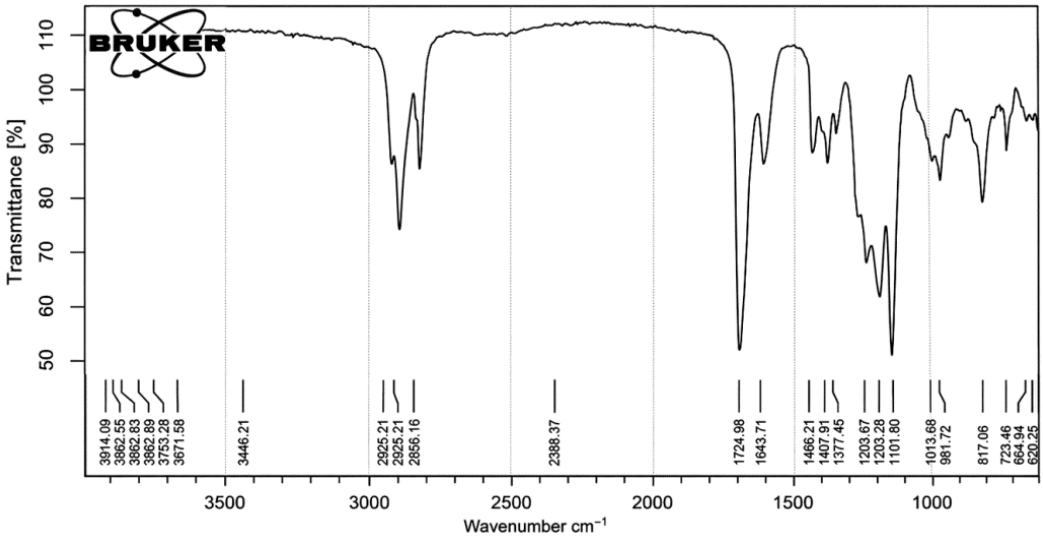

Fig. 5 — FT-IR of compound 2

***In vivo* study**

During the acute dermal toxicity study, no toxic symptoms were observed on the skin of Female rats; however, animals were continuously monitored during the study till 14th day. The body weight was found to slightly increase as rats were given access to a standard diet. Accordingly, two suitable doses were selected for the mouse tail model of psoriasis for further evaluation (Figs. 11-12, and Table 7).

In histopathological examination, it was observed that in the control group, the mouse tail contains all the salient features of psoriasis, such as the presence of a parakeratosis layer, Munro's microabscesses, capillary loop dilation, and elongation of rete ridges. Moreover, in the vehicle control group, a similar set of features was observed. In contrast, in the standard group, except for capillary loop dilation, these cardinal signs of psoriasis were absent. In compound-treated groups, we observed that compound 2-treated animals at the 50 mg/kg dose, except for capillary loop dilation, showed almost complete disappearance of all psoriasis features. However, a 100 mg/kg dose of compound 2 significantly reduces the capillary loop dilation in the tails. In compound 3 at 50 and 100 mg/kg doses, except for the elongation of rete ridges, all features of psoriasis were profoundly present. Similarly, in compound 4, at both doses, all features were present, but rete ridges elongation was found to be absent. Hence, compound 2 at 100 mg/kg was found to be more effective compared to other synthetic compounds, demonstrating efficiency in an *in vivo* study by enhancing orthokeratosis and reducing parakeratosis on the mouse tail. The structure-activity relationship study, on the basis of molecular docking and *in vivo* results, indicates that the compounds with long aliphatic chains demonstrated better *in silico* and *in vivo* activity; however, aryl compounds showed better activity compared to cyclic compounds.

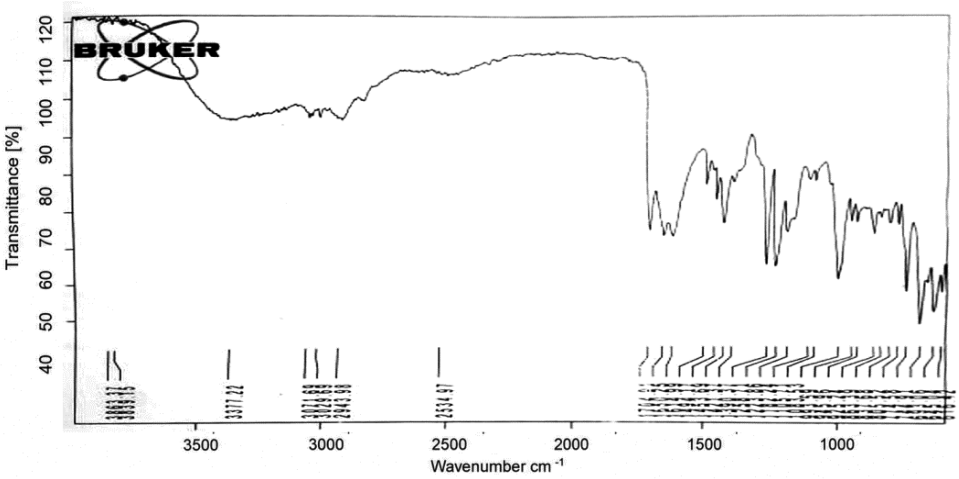

Fig. 6 — FT-IR of compound 3

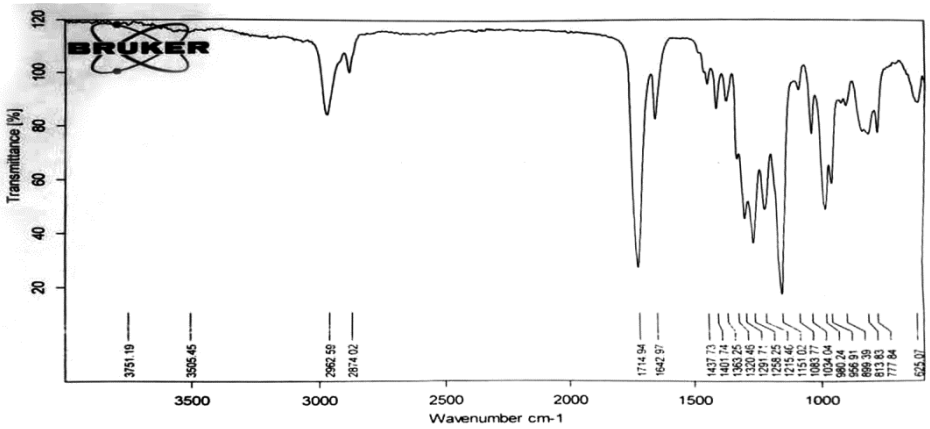

Fig. 7 — FT-IR of compound 4

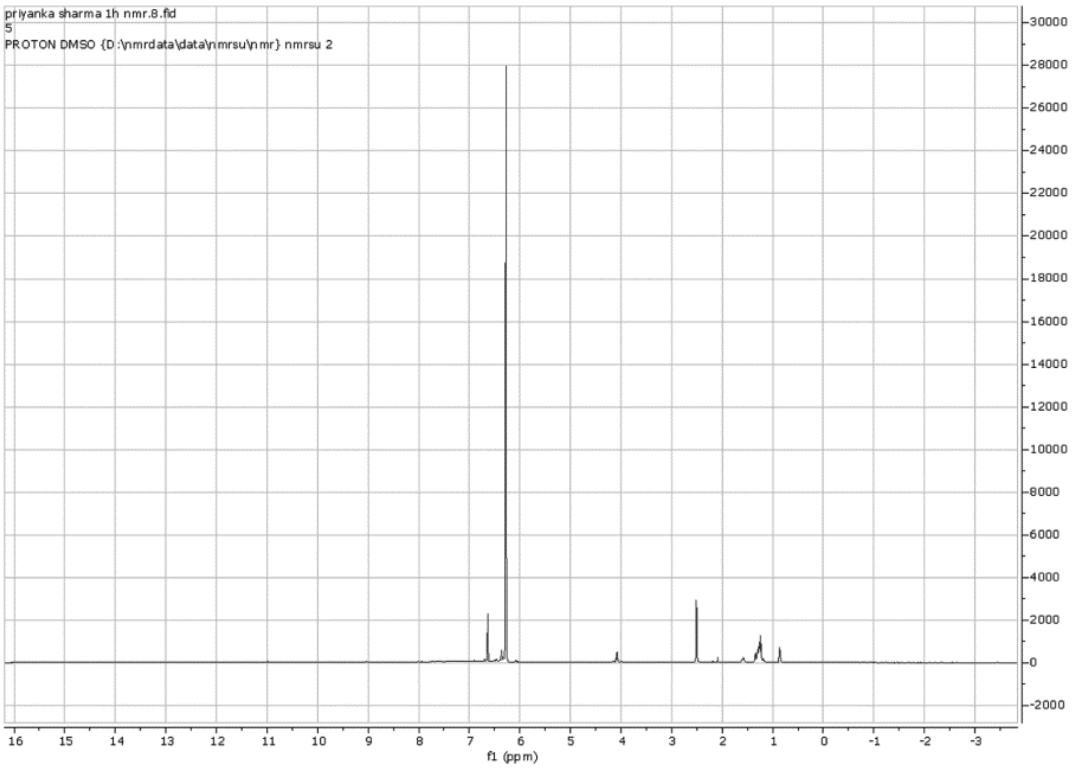

Fig. 8 — Compound 2 1HNMR: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.44 – 6.28 (m, 2H), 4.11 (dt, J = 26.5, 6.6 Hz, 2H), 1.59 (h, J = 6.7 Hz, 2H), 1.28 (d, J = 9.7 Hz, 5H), 1.25 (s, 6H), 0.85 (t, J = 6.4 Hz, 3H)

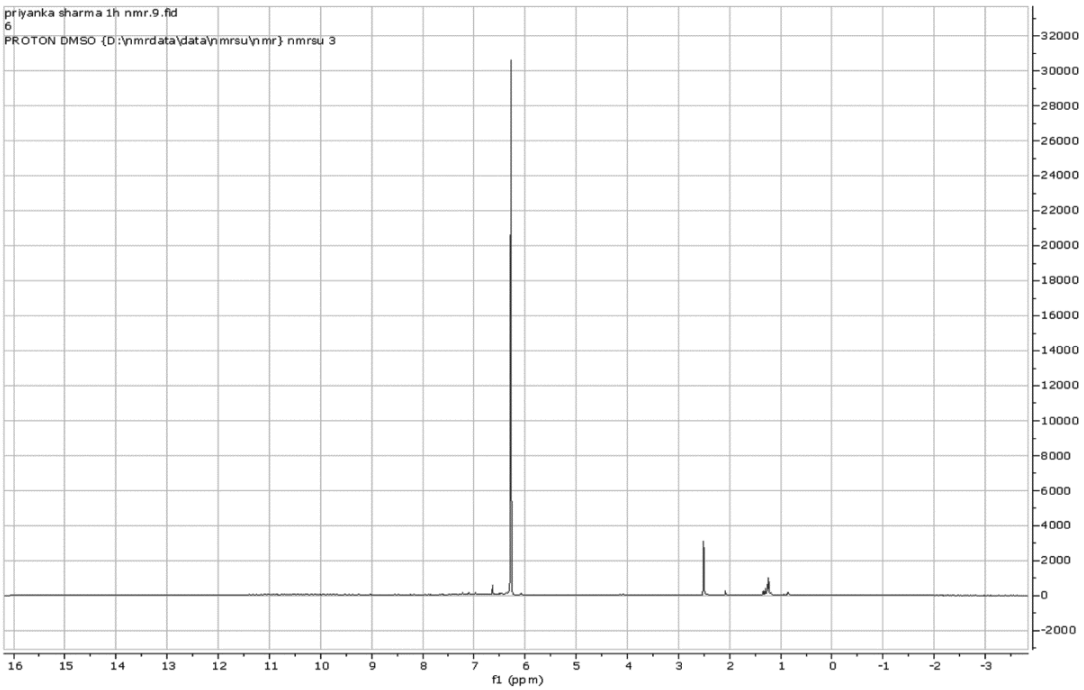

Fig. 9 — Compound 3 ^{1}H NMR: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.30 (m, 13H), 7.32 – 7.26 (m, 1H), 7.05 (s, 1H), 7.00 (s, 1H), 3.01 (s, 1H), 2.93 (s, 1H), 1.39 – 1.26 (m, 2H)

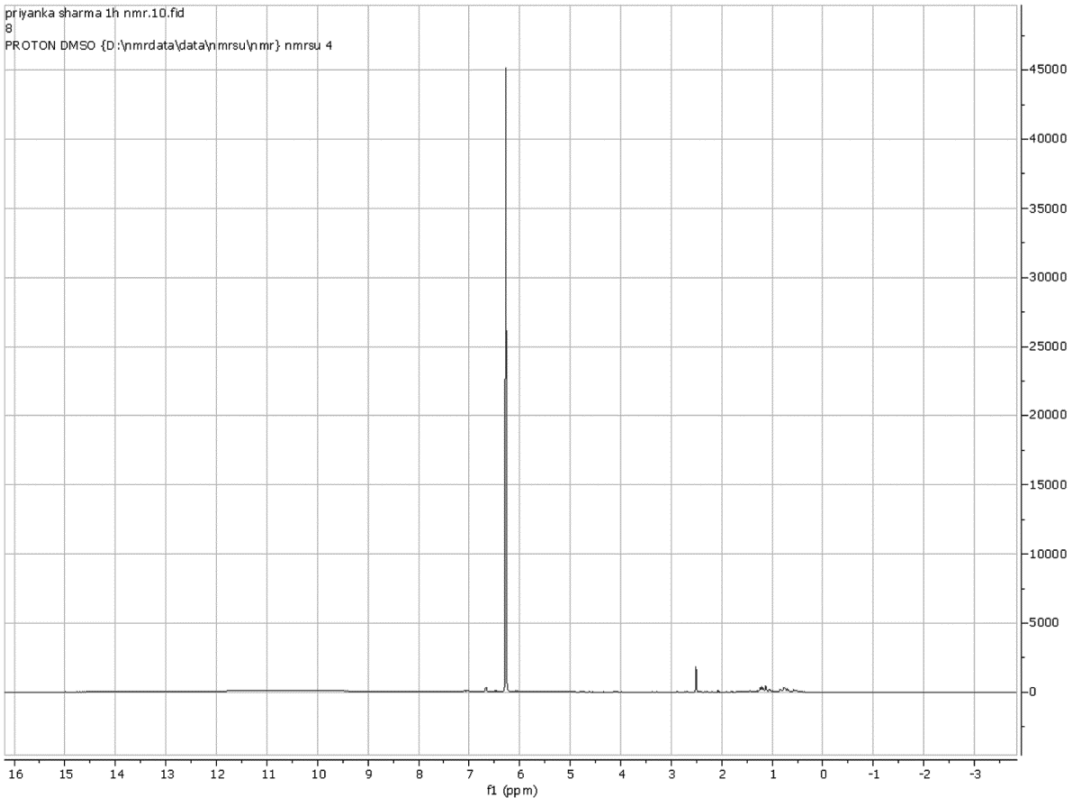

Fig. 10 — Compound 4 ^{1}H NMR: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.88 – 6.71 (m, 4H), 5.22 (d, *J* = 6.1 Hz, 3H), 1.84 (dq, *J* = 15.5, 9.2, 7.5 Hz, 5H)

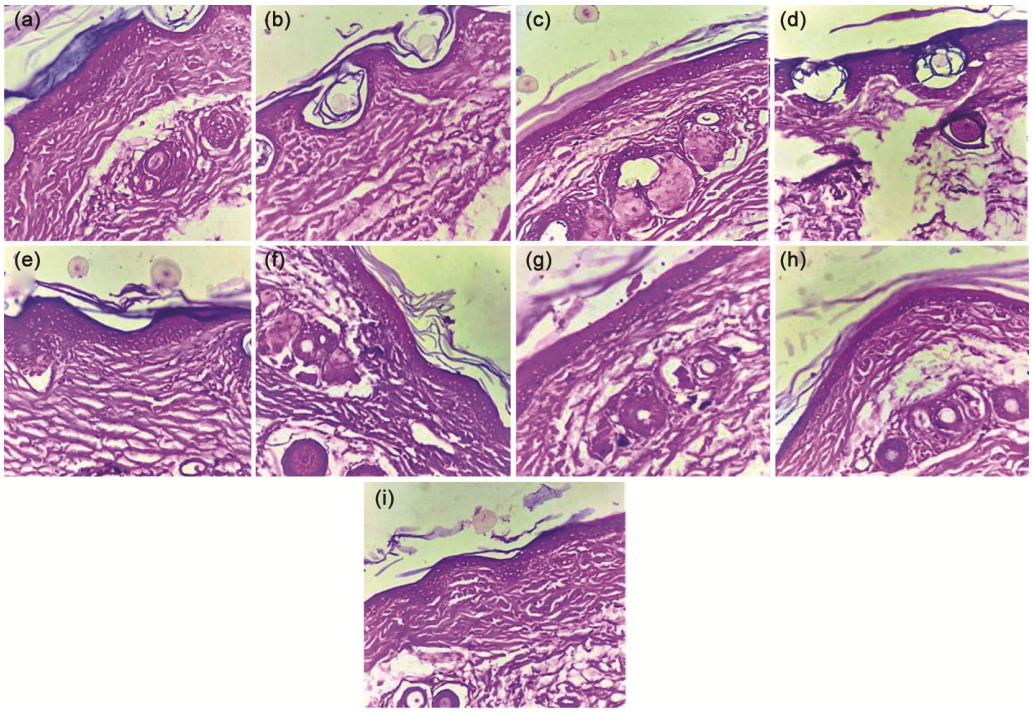

Fig. 11 — Histopathological section examination of mouse tail (a) Control; (b) Standard (Clobetasol propionate 0.5%); (c) Vehicle treated; (d) Compound 2 50 mg/kg; (e) Compound 2 1000 mg/kg; (f) Compound 3 50 mg/kg; (g) Compound 3 100 mg/kg; (h) Compound 4 50 mg/kg; and (i) Compound 4 100 mg/kg)

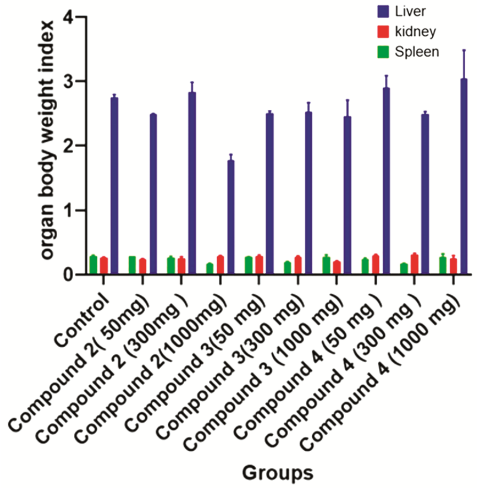

Fig. 12 — Organ body weight index, $P > 0.05$, was found to be non-significant when compared with control

Table 5 — Percentage yield and reaction condition

S. No	Compound	% Yield	Reaction conditions
1	Compound 2	88%	The reaction occurred at 160°C in the presence of iodine as a catalyst
2	Compound 3	69.4%	The reaction occurred at 70-75°C in the presence of ammonium chloride as a catalyst
3	Compound 4	75.7%	The reaction occurred at 160°C in the presence of iodine as a catalyst

Table 6 — Evaluation parameters of formulation study

Batch	pH	Spreadability (g.cm/sec)	Viscosity (dyne·s/cm^2)	Homogeneity
F1	6.8± 0.34	28.34± 1.04	35732±13.35	Clear

Table 7 — Mean and standard deviation of organ weight index

Groups	Liver body weight index	Kidney body weight index	Spleen body weight index
Control	2.75±0.04	0.26±0.005	0.282±0.015
Compound 2 (50 mg)	2.49±0.01	0.24±0.002	0.28±0
Compound 2 (300 mg)	2.83±0.15	0.25±0.024	0.263±0.0165
Compound 2 (1000 mg)	1.77±0.09	0.27±0.013	0.1661±0.0078
Compound 3 (50 mg)	2.50±0.03	0.27±0.023	0.272±0.0021
Compound 3 (300 mg)	2.52±0.14	0.27±0.010	0.187±0.01296
Compound 3 (1000 mg)	2.46±0.25	0.20±0.006	0.270±0.0336
Compound 4 (50 mg)	2.90±0.18	0.29±0.021	0.239±0.0170
Compound 4 (300 mg)	2.48±0.04	0.30±0.018	0.171±0.001
Compound 4 (1000 mg)	3.03±0.44	0.25±0.039	0.276±0.0427

Conclusion

The present research was designed to explore the synthesis and evaluation of novel analogues of Fumaric Acid Esters (FAEs) with potential anti-psoriatic activity, specifically targeting the P38-MAPK pathway, a key regulator of pro-inflammatory cytokines and chemokines involved in psoriasis pathogenesis[29,30]. Psoriasis is a multifactorial, immune-mediated skin disorder characterised by chronic inflammation, abnormal keratinocyte proliferation, and systemic involvement. Advances in the understanding of its genetic and immunological basis have led to more precise and targeted therapeutic strategies. While conventional treatments such as corticosteroids, phototherapy, and systemic agents remain effective, they are often associated with adverse effects and poor long-term compliance. In this context, FAEs—particularly Dimethyl Fumarate (DMF)—have demonstrated notable efficacy in modulating immune responses[31]. However, side effects such as gastrointestinal disturbances and rare cases of lymphopenia and hepatotoxicity have necessitated the development of novel analogues with improved safety and efficacy profiles. In this study, a series of fumaric acid ester analogues was designed, synthesised, and characterised using spectroscopic techniques. *In silico* analysis confirmed drug-likeness and favourable pharmacokinetics. Selected compounds were further evaluated using molecular docking, acute dermal toxicity, and the mouse tail model for anti-psoriatic activity. Among the tested analogues, Compound 2 exhibited the most promising profile, demonstrating High binding affinity for P38-MAPK, Good absorption through topical gel formulation, Absence of dermal or systemic toxicity and Effective restoration of normal keratinization *in vivo*. These findings support the hypothesis that structural modification of FAEs can enhance therapeutic potential while minimizing adverse effects.

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Conflict of interest

All authors declare no conflict of interest.

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