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Original Article

Docking Analysis of 18 Selected Dalethyne Derivatives as Human Neutrophil Elastase, Hyaluronidase and Tyrosinase Related Protein 1 Modulating Agents

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ABSTRACT

Background: Dalethyne (DE) is unique multicomponent chemical substance, which is rich in peroxides, aldehydes, anisidines, and iodine bearing moieties. Dalethyne (DE) has been reported to possess various pharmaceuticals activities like anti-fungal, anti-microbial, anti-septic, anti-viral and wound healing. **Objectives:** In the current study, we aimed to evaluate 18 selected Dalethyne (DE) derivatives as potent modulating agents of Human Neutrophil Elastase (hNE), hyaluronidase (hHyal) and Tyrosinase Related Protein 1 (hTYRP1) using docking approach. **Materials and Methods:** The eighteen chosen Dalethyne (DE) derivatives (ligands) were investigation on the docking behaviour of Human Neutrophil Elastase (hNE), hyaluronidase (hHyal) and Tyrosinase Related Protein 1 (hTYRP1) by using the Swiss dock method. **Results:** The docking analysis showed that Methyl stearate, Methyl arachidate and Methyl octadec-8-enoate of Dalethyne (DE) ligand has exhibited highest binding energy (-8.19, -8.51 and -8.48 kcal/mol) with hNE, hHYAL and hTYRP1 respectively. **Conclusion:** Thus, the present findings provide new insight of these 18 selected Dalethyne derivatives (ligands) as potent (hNE, hHYAL and hTYRP1) modulating agents, which will aid in managing good health and well-being, particularly cancer, inflammation, photo aging, pigmentation and wounds.

Keywords: Dalethyne, Docking, Good Health and Well-being, Human Hyaluronidase, Human Neutrophil Elastase, Human Tyrosinase Related Protein 1.

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INTRODUCTION

Dalethyne (DE) is an emergent bioactive compound and it is the molecular scaffold derived through the controlled transformation of the Long-Chain Fatty Acids, (LCFA) prominently originating from Virgin Olive Oil (VOO). This is a unique multicomponent chemical profile which comprises of i) peroxides, ii) aldehydes, iii) anisidines, and iv) iodine-bearing moieties-positions. Dalethyne (DE) derivatives have been reported as a potent antimicrobial agent and a modulator of complex biological wound healing pathways (Dharshan, 2019). The antimicrobial efficacy of the Dalethyne (DE) derivatives has been reported due to iodine-based oxidative antimicrobial activity and iodine-based antiseptic activity. This in turn disrupts microbial membranes particularly biofilms without significant bacterial resistance development. Moreover, iodine-based products have been reported to exhibit a wide spectrum activity against i) bacteria, ii) fungi, iii) viruses, and iv) protozoa, and consistently reduce wound bio burden in both acute and chronic wound patients (Bigliardi *et al*., 2017).

In addition to direct antimicrobial actions of Dalethyne (DE) derivatives, the wound healing critically depends upon the regulatory mechanism of the oxidative stress and the cytokine balance. Moderate Reactive Oxygen Species (ROS) generation acts as a signalling cue to recruit inflammatory cells and myofibroblasts, while excessive ROS can undermine matrix deposition and cellular viability (Mohite *et al*., 2025). These bioactivities support the rationale for dalethyne's foundational design, which integrates oxidative functions and potential iodine-mediated microbiocidal actions within a lipid scaffold to create a conducive environment for repair. Although the exact molecular mechanisms of Dalethyne (DE) derivatives remain to be fully elucidated, it is observed *in vivo* effects on bacterial burden and early healing markers align with established bioactive paradigms in wound science (Arozal *et al*., 2020).

Olive Oil (OO) and its phenolic components such as hydroxytyrosol have been shown in diabetic wound models to enhance collagen deposition, anti-inflammatory macrophage polarization, fibroblast migration, and pro-healing mediator

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expression (Duarte *et al.*, 2024). Dalethyne's (DE) modulatory effect on infiltrating immune cells and macrophage activity observed histologically parallels the therapeutic goals of advanced wound treatments that balance microbial suppression with controlled inflammation (Moni *et al.*, 2022).

Comparative analyses with conventional antiseptic and wound-healing agents reveal that Dalethyne (DE) derivatives not only exhibits broad-spectrum antimicrobial efficacy, drug-resistant gram-negative bacteria, but also outperforms the phenol benchmarks at equal concentrations (Dharshan, 2019). Dalethyne (DE) derivatives have been explored using *in silico* molecular docking, revealing significant binding affinities against key enzymes involved in tissue regeneration and modulation of inflammation (Dharshan, 2018).

The previous reports engaged us to carry out the present investigation on the eighteen chosen Dalethyne (DE) derivatives which includes Dimethyl azelate; 6,6-Dimethoxy-octanoic acid; Dimethyl suberimidate; Dimethyl undecanedioate; Methyl arachidate; Methyl behenate; Methyl decanoate; Methyl 8,8-dimethoxyoctanoate; Methyl 11-eicosenoate; Methyl linoleate; Methyl myristate; Methyl nonanoate; Methyl octadec-8-enoate; Methyl 8-[(1s,2r)-2-octylcyclopropyl] octanoate; Methyl oleate; Methyl 9-oxononanoate; Methyl palmitate; Methyl stearate, on two reference compounds- Oleocanthal; Oleuropein and on one standard compound- Tyrosol.

MATERIALS AND METHODS

Ligand preparation

The chemical structures of eighteen (Dalethyne (DE) derivatives) ligands were selected based on the previous report (Dharshan, 2018), which includes 1) Dimethyl azelate (CID no 15612), 2) 6,6-Dimethoxy-octanoic acid (CID no 131839788), 3) Dimethyl suberimidate (CID no 34750), 4) Dimethyl undecanedioate (CID no 78321), 5) Methyl arachidate (CID no 14259), 6) Methyl behenate (CID no 13584), 7) Methyl decanoate (CID no 8050), 8) Methyl 8,8-dimethoxyoctanoate (CID no 554817), 9) Methyl 11-eicosenoate (CID no 102251), 10) Methyl linoleate (CID no 5284421), 11) Methyl myristate (CID no 31284), 12) Methyl nonanoate (CID no 15606), 13) Methyl octadec-8-enoate (CID no 543299), 14) Methyl 8-[(1s,2r)-2-octylcyclopropyl]octanoate (CID no 107485), 15) Methyl oleate (CID no 5364509), 16) Methyl 9-oxononanoate (CID no 74732), 17) Methyl palmitate (CID no 8181), 18) Methyl stearate (CID no 8201), 19) Reference compound-1: Oleocanthal (CID no 11652416), 20) Reference compound-2: Oleuropein (CID no 5281544), 21) Standard-Tyrosol (CID no 10393) were downloaded from PubChem compound database. The Dalethyne (DE) ligands structures were drawn and prepared by using ChemDraw 2D and 3D software tools (Kumaraswamy *et al.*, 2023). Thus, these prepared three-dimensional structures were used for further studies swissdock.

Preparation of target enzymes

The 3D structures of the Human Neutrophil Elastase (hNE), Human Hyaluronidase (hHyal) and Human Tyrosinase Related Protein 1 (hTYRP1) were retrieved from the Protein Data Bank (PDB) as target docking enzymes (Macdonald *et al.*, 2002; Chao *et al.*, 2007; Lai *et al.*, 2017), (https://www.rcsb.org/structure; pdb code: 1H1B, 2PE4, 5M8L). The 'A' chain of these enzymes was prepared independently by deleting the other chains, ligands, and even the crystallographically observed 'water' (H_2O) molecules by using UCSF Chimera software tool (Rajagopal *et al.*, 2024).

ADMET analysis

SwissADME free web server was utilized to analyse the ADME (Absorption, Distribution, Metabolism, Excretion) of the eighteen selected (Dalethyne (DE) ligands (Daina *et al.*, 2017), similarly Protox3.0 free online software tool was used to analyse the toxicity of the selected 18 ligands (Banerjee *et al.*, 2018).

Docking study

A molecular docking study is an *in silico* approach that predicts the preferred orientation, binding mode, and binding affinity of a ligand when it interacts with a biological target, aiding to infer the strength and specificity of molecular interactions relevant to the ligand (drug) action. In the current study, docking analysis was carried out for eighteen chosen Dalethyne (DE) derivatives with three target enzymes (Human Neutrophil Elastase (hNE), Human Hyaluronidase (hHyal) and Human Tyrosinase Related Protein 1 (hTYRP1)) using the Swissdock (http://old.swissdock.ch/) free online server (Prakash *et al.*, 2023). Finally, PLIP (Protein ligand interaction profiler) web server was used to analyse the binding site of the best-docked pose for each ligand (Prakash *et al.*, 2023). In current investigation, no experimental animals (or) human subjects were utilized; hence ethical approval was not applicable.

With regard to statistical analysis, in the current study tyrosol (standard drug) was used for the comparison purpose. And the Root Mean Square Deviation ($RMSD^a$) analysis of all the docked complexes was individually compared with that of tyrosol (standard drug) docked complex for each target enzyme, by using the 'align' command in "PyMOL" software. The Root Mean Square Deviation ($RMSD^a$) analysis reveals that if $RMSD^a$ less than (or) equal to 2.0 A^o it is considered as 'excellent'; whereas if $RMSD^a$ greater than 2.0 and less than 3.0 A^o then it is indicated as 'fair'. On the other hand, if $RMSD^a$ greater than (or) equal to 3.0 A^o it is considered as 'poor' (Ramsbottom *et al.*, 2018, Narayanaswamy *et al.*, 2024).

RESULTS

Table 1 represents the Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) analysis of eighteen selected Dalethyne (DE) derivatives (ligands) using the Swiss ADME and Protox3.0 online software. Four ligands (Methyl arachidate,

Methyl behenate, Methyl 11-eicosenoate, Oleuropein) exhibits low gastro-intestinal absorption, whereas all the other ligands show high gastro-intestinal absorption. On the other hand, all the ligands do not show the cytochrome CYP2C194 property. The ligand (Oleuropein) shows the maximum value of -9.92 cm/s for skin permeation, whereas the ligand (Methyl behenate) shows the least skin permeation value of -1.22 cm/s. All the ligands do not exhibit any of the hepatotoxicity nature (as shown in Table 1).

In the current study, Oleuropein (reference compound 2) has exhibited the highest binding energy (-8.27 kcal/mol) with the Human Neutrophil Elastase (hNE). In contrast to this, the least binding energy with the Human Neutrophil Elastase (hNE) is seen in the Tyrosol (-5.95 kcal/mol) as shown in Table 2. Five ligands (Dimethyl azelate, 6,6-Dimethoxy-octanoic acid, Methyl arachidate, Methyl myristate, Methyl myristate) have shown interactions with SER 195 amino acid residues of Human Neutrophil Elastase (hNE). Similarly, five ligands (Methyl behenate, Methyl decanoate, Methyl palmitate, Oleocanthal, Tyrosol) exhibited interactions with VAL 216 amino acid residue of the Human Neutrophil Elastase (hNE). On the other hand, three ligands (Dimethyl azelate, Methyl 8,8-dimethoxyoctanoate, Methyl myristate) have shown interactions with the ASN 61 amino acid residue of Human Neutrophil Elastase (hNE). However, eight ligands (Dimethyl undecanedioate, Methyl 11-eicosenoate, Methyl linoleate, Methyl nonanoate, Methyl octadec-8-enoate, Methyl 8-[(1s,2r)-2-octylcyclopropyl] octanoate, Methyl oleate, Methyl stearate) did not show any hydrogen bond interaction with the Human Neutrophil Elastase (hNE).

Table 1: Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) analysis of 18 selected Dalethyne derivatives using SwissADME and Protox 3.0 software tools.

Ligand	GI[a]	BBB[b]	P-gp[c]	CYP1A2[d]	CYP2C19[e]	CYP2C9[f]	CYP2D6[g]	CYP3A4[h]	Log Kp[i] (cm/s)	HT[k]
Dimethyl azelate	H[l]	Y[m]	N[n]	N[n]	N[n]	N[n]	N[n]	N[n]	-5.87	IA[o]
6,6-Dimethoxy-octanoic acid	H[l]	Y[m]	N[n]	N[n]	N[n]	N[n]	N[n]	N[n]	-6.57	IA[o]
Dimethyl suberimidate	H[l]	Y[m]	N[n]	N[n]	N[n]	N[n]	N[n]	N[n]	-6.21	IA[o]
Dimethyl undecanedioate	H[l]	Y[m]	N[n]	N[n]	N[n]	N[n]	N[n]	N[n]	-5.27	IA[o]
Methyl arachidate	L[P]	N[n]	N[n]	Y[m]	N[n]	N[n]	N[n]	N[n]	-1.69	IA[o]
Methyl behenate	L[P]	N[n]	N[n]	Y[m]	N[n]	N[n]	N[n]	N[n]	-1.22	IA[o]
Methyl decanoate	H[l]	Y[m]	N[n]	N[n]	N[n]	N[n]	N[n]	N[n]	-4.31	IA[o]
Methyl 8,8-dimethoxyoctanoate	H[l]	Y[m]	N[n]	N[n]	N[n]	N[n]	N[n]	N[n]	-6.16	IA[o]
Methyl 11-eicosenoate	L[P]	N[n]	N[n]	Y[m]	N[n]	N[n]	N[n]	N[n]	-2.43	IA[o]
Methyl linoleate	ND[q]	ND[q]	ND[q]	ND[q]	ND[q]	ND[q]	ND[q]	ND[q]	ND[q]	IA[o]
Methyl myristate	H[l]	Y[m]	N[n]	Y[m]	N[n]	N[n]	N[n]	N[n]	-3.23	IA[o]
Methyl nonanoate	H[l]	Y[m]	N[n]	N[n]	N[n]	N[n]	N[n]	N[n]	-4.28	IA[o]
Methyl octadec-8-enoate	H[l]	N[n]	N[n]	Y[m]	N[n]	N[n]	N[n]	N[n]	-2.82	IA[o]
Methyl 8-[(1s,2r)-2-octylcyclopropyl] octanoate	H[l]	N[n]	N[n]	Y[m]	N[n]	Yes	N[n]	N[n]	-2.29	IA[o]
Methyl oleate	H[l]	N[n]	N[n]	Y[m]	N[n]	N[n]	N[n]	N[n]	-2.82	IA[o]
Methyl 9-oxononanoate	H[l]	Y[m]	N[n]	N[n]	N[n]	N[n]	N[n]	N[n]	-5.99	IA[o]
Methyl palmitate	H[l]	Y[m]	N[n]	Y[m]	N[n]	N[n]	N[n]	N[n]	-2.71	IA[o]
Methyl stearate	H[l]	N[n]	N[n]	Y[m]	N[n]	N[n]	N[n]	N[n]	-2.19	IA[o]
Oleocanthal	H[l]	N[n]	N[n]	N[n]	N[n]	N[n]	N[n]	N[n]	-7.11	IA[o]
Oleuropein	L[P]	N[n]	Y[m]	N[n]	N[n]	N[n]	N[n]	N[n]	-9.92	IA[o]
Tyrosol	H[l]	Y[m]	N[n]	N[n]	N[n]	N[n]	N[n]	N[n]	-6.84	IA[o]

Note: GI[a]- Gastrointestinal absorption, BBB[b]- Blood-brain barrier permeant, P-gp[c]- P-glycoprotein substrate, CYP1A2[d] - Cytochrome P450 family 1 subfamily A member 2 inhibitors, CYP2C19[e]- Cytochrome P450 family 2 subfamily C member 19 inhibitors, CYP2C9[f]- Cytochrome P450 family 2 subfamily C member 9 inhibitors, CYP2D6[g]- Cytochrome P450 family 2 subfamily D member 6 inhibitors, CYP3A4[h]- Cytochrome P450 family 3 subfamily A member 4 inhibitors, Log Kp[i] - Skin Permeation (cm/s), HT[k]- Hepatotoxicity, H[l]- High, Y[m]- Yes, N[n]- No, IA[o]- In active, L[P]- Low, ND[q]- Not determine

Table 2: Binding energy analysis of eighteen selected Dalethyne derivatives with human Neutrophil Elastase (hNE) using Swissdock web server.

Sl. No.	Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance H-A (A°)	Bond distance D-A (A°)	RMSD[a] compared with Tyrosol docked complex (A°)
1.	Dimethyl azelate	6.75	ASN 61 SER 195	1.89 3.30	2.80 3.80	0.56
2.	6,6-Dimethoxy-octanoic acid	6.46	SER 195	2.47, 2.87	3.36, 3.55	0.47
3.	Dimethyl suberimidate	7.06	PHE 41 HIS 57 CYS 191	2.38 3.30 3.26	3.29 3.70 4.01	0.87
4.	Dimethyl undecanedioate	6.78	NI[b]	-	-	0.48
5.	Methyl arachidate	8.08	SER 195	3.25	3.86	0.83
6.	Methyl behenate	8.07	VAL 216	3.21	3.90	0.99
7.	Methyl decanoate	6.71	VAL 216	3.05	3.49	0.52
8.	Methyl 8,8-dimethoxyoctanoate	6.87	ASN 61	1.81	2.78	0.54
9.	Methyl 11-eicosenoate	7.82	NI[b]	-	-	0.97
10.	Methyl linoleate	7.91	NI[b]	-	-	0.85
11.	Methyl myristate	7.23	GLY 193 SER 195	3.00 3.15	3.88 3.46	0.79
12.	Methyl nonanoate	6.80	NI[b]	-	-	0.63
13.	Methyl octadec-8-enoate	7.84	NI[b]	-	-	0.58
14.	Methyl 8-[(1s,2r)-2-octylcyclopropyl] octanoate	7.60	NI[b]	-	-	0.64
15.	Methyl oleate	7.10	NI[b]	-	-	0.83
16.	Methyl 9-oxononanoate	6.45	ASN 61 SER 195	2.21 2.51	3.00 3.47	0.63
17.	Methyl palmitate	7.38	VAL 216	3.05	3.41	0.70
18.	Methyl stearate	8.19	NI[b]	-	-	0.95
19.	Oleocanthal	7.31	VAL 216	2.85	3.71	0.93
20.	Oleuropein	8.27	HIS 40	2.30	3.18	0.62
21.	Tyrosol	5.95	VAL 216	2.85	3.71	-

NOTE: RMSD[a]- Root mean square deviation, NI[b]-No hydrogen bond interactions.

Similarly, in the present study, Oleuropein (reference compound 2) has exhibited the highest binding energy (-8.54 kcal/mol) with the human hyaluronidase. In contrast to this, the least binding energy with the human hyaluronidase has shown by Tyrosol (-6.52 kcal/mol) as mentioned in the Table 3. Four ligands (6,6-Dimethoxy-octanoic acid, Methyl decanoate, Methyl linoleate, Methyl nonanoate) have shown interactions with GLN 64 amino acid residue of human hyaluronidase. On the other hand, three ligands (Dimethyl azelate, Dimethyl suberimidate, Dimethyl undecanedioate) have shown interactions with GLY 68 amino acid residue, similarly another three ligands (Methyl decanoate, Methyl nonanoate, Tyrosol) have shown interactions with PHE 66 amino acid residue of human hyaluronidase. Two ligands (6,6-Dimethoxy-octanoic acid, Dimethyl suberimidate) have shown interactions with ASN 61 amino acid residues, whereas another pair of ligands (6,6-Dimethoxy-octanoic acid, Methyl linoleate) have shown interactions with ILE 73 amino acid residues. Similarly, two ligands (Dimethyl suberimidate, Methyl myristate) exhibited interactions with the MET 71 amino acid residues, whereas another set of two ligands (Methyl decanoate, Methyl nonanoate) have shown interactions with THR 65 amino acid residues. A pair of two ligands (Methyl 9-oxononanoate, Oleuropein) exhibited interactions with ARG 419 amino acid residues of human hyaluronidase. However, seven ligands (Methyl arachidate, Methyl behenate, Methyl 8,8-dimethoxyoctanoate, Methyl 11-eicosenoate, Methyl oleate, Methyl palmitate, Methyl

Table 3: Binding energy analysis of eighteen selected Dalethyne derivatives with human Hyaluronidase (hHyal) using Swissdock web server.

Sl. No.	Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance H-A (A°)	Bond distance D-A (A°)	RMSD[a] compared with Tyrosol docked complex (A°)
1.	Dimethyl azelate	7.20	ARG 67 GLY 68	2.86 2.42	3.82 3.35	0.30
2.	6,6-Dimethoxy-octanoic acid	6.82	ASN 61 GLN 64 ILE 73	3.18 2.69 2.18	3.51 3.62 2.99	0.59
3.	Dimethyl suberimidate	7.26	ASN 61 GLY 68 MET 71 GLN 78	2.96 3.08 2.25 3.59	3.49 3.91 3.26 3.98	0.31
4.	Dimethyl undecanedioate	7.46	GLY 68	2.46	3.39	0.30
5.	Methyl arachidate	8.51	NI[b]	-	-	0.71
6.	Methyl behenate	8.15	NI[b]	-	-	2.75
7.	Methyl decanoate	6.90	GLN 64 THR 65 PHE 66	3.61 3.05 3.13	3.96 3.72 4.03	0.59
8.	Methyl 8,8-dimethoxyoctanoate	7.23	NI[b]	-	-	0.34
9.	Methyl 11-eicosenoate	8.50	NI[b]	-	-	0.87
10.	Methyl linoleate	8.23	GLN 64 ILE 73	2.73 2.26	3.65 3.11	0.81
11.	Methyl myristate	7.55	MET 71	3.39	3.95	0.74
12.	Methyl nonanoate	6.75	GLN 64 THR 65 PHE 66	3.62 3.08 3.15	3.98 3.75 4.06	0.55
13.	Methyl octadec-8-enoate	7.68	ASP 70	2.87	3.69	0.70
14.	Methyl 8-[(1s,2r)-2-octylcyclopropyl] octanoate	7.90	GLU 268	3.43	3.77	2.61
15.	Methyl oleate	8.23	NI[b]	-	-	0.58
16.	Methyl 9-oxononanoate	6.87	GLN 263 ARG 371 ARG 419	2.87 2.09 3.17	3.50 2.91 4.01	2.41
17.	Methyl palmitate	7.63	NI[b]	-	-	0.43
18.	Methyl stearate	7.30	NI[b]	-	-	2.60
19.	Oleocanthal	8.04	GLU 304 LEU 381	1.81 3.15	2.78 3.78	2.76
20.	Oleuropein	8.54	GLN 313 ARG 419	2.74, 2.12 2.62	3.18, 2.98 3.38	2.59
21.	Tyrosol	6.52	PHE 66	1.96	2.90	-

NOTE: RMSD[a]- Root mean square deviation, NI[b]-No hydrogen bond interactions.

stearate) did not show any hydrogen bond interaction with the human hyaluronidase.

In the present study, Methyl octadec-8-enoate has exhibited the highest binding energy (-8.48 kcal/mol) with the Human Tyrosinase Related Protein 1 (hTYRP1). In contrast to this, the least binding energy with the Human Tyrosinase Related Protein 1 (hTYRP1) is seen in the Methyl nonanoate (-6.69 kcal/mol) as shown in the Table 4. Six ligands (Dimethyl azelate, Dimethyl suberimidate, Methyl arachidate, Methyl 8, 8-dimethoxyoctanoate, Methyl 8-[(1s,2r)-2-octylcyclopropyl] octanoate, Tyrosol-standard) have shown interactions with GLY 116 amino acid residue of Human Tyrosinase Related Protein 1 (hTYRP1). Similarly, two ligands (Dimethyl azelate, Methyl decanoate) have shown interactions with TYR 226 amino acid residue, whereas two ligands (Dimethyl suberimidate, Tyrosol) have shown interactions with CYS 113 amino acid residue of (hTYRP1). However, eight ligands (Dimethyl undecanedioate, Methyl behenate, Methyl 11-eicosenoate, Methyl linoleate, Methyl octadec-8-enoate, Methyl oleate, Methyl palmitate, Methyl stearate) did not show any hydrogen bond interaction with the Human Tyrosinase Related Protein 1 (hTYRP1).

DISCUSSION

Dalethyne (DE) has unique multicomponent chemical profile-rich in peroxides, aldehydes, anisidines, and iodine-bearing moieties, which possess both a potent antimicrobial activity and a modulator of complex, wound repair pathways (Dharshan, 2019). Moreover, selected ligands of Dalethyne (DE) derivatives do not have any hepatotoxicity property.

In the current investigation, all the selected ligands of Dalethyne (DE) derivatives have successfully docked with the human neutrophil elastase enzyme. The swissdock binding energy ranges from the highest Oleuropein (-8.27 kcal/mol) to the lowest Tyrosol (-5.95 kcal/mol). More the negative value of the binding energy indicates more its affinity towards the target enzyme 1 (human neutrophil elastase). The three chosen Dalethyne (DE) ligands (Dimethyl azelate, Methyl 8, 8-dimethoxyoctanoate, Methyl 9-oxononanoate) have shown interactions with ASN 61 amino acid residues of human neutrophil elastase enzyme. This result showed good correlation with the earlier reports (Ragavan *et al.*, 2020). Similarly, one ligand (Dimethyl suberimidate) has shown interactions with HIS 57 amino acid residues with hNE enzyme, which is on par with the published, report (Narayanaswamy *et al.*, 2014). Also, the same ligand (Dimethyl suberimidate) has shown interactions with CYS 191 amino acid residues of the human neutrophil elastase enzyme, which follows the recent research paper (Narayanaswamy *et al.*, 2023).

In this study, five selected Dalethyne (DE) ligands (Dimethyl azelate, 6, 6-Dimethoxy-octanoic acid, Methyl arachidate, Methyl myristate, Methyl 9-oxononanoate) have exhibited hydrogen bond interactions with the SER 195 amino acid residues of the human neutrophil elastase enzyme, which is in accordance with the previously published reports (Narayanaswamy *et al.*, 2014; Narayanaswamy *et al.*, 2023). Similar to this, five Dalethyne (DE) ligand derivatives (Methyl behenate, Methyl decanoate, Methyl palmitate, Oleocanthal, Tyrosol) have displayed interactions with the VAL 216 amino acid residues of the human neutrophil enzyme. This result is in excellent correlation with earlier reports (Narayanaswamy *et al.*, 2014; Ragavan *et al.*, 2020; Narayanaswamy *et al.*, 2023). One Dalethyne (DE) ligand (Methyl myristate) has shown hydrogen bond interaction with the GLY 193 amino acid residue of hNE enzyme, which is in accordance with the recent research report (Narayanaswamy *et al.*, 2023).

In the present docking study, all the chosen Dalethyne (DE) ligands have successfully docked with the human hyaluronidase enzyme. The swissdock binding energy ranges from the lowest Tyrosol (-6.52 kcal/mol) to the highest Oleuropein (-8.54 kcal/mol). More the negative value of the binding energy indicates more its affinity towards the target enzyme 2 (human hyaluronidase). The two chosen Dalethyne (DE) ligands (Dimethyl suberimidate and Methyl myristate) have shown interactions with the MET 71 amino acid residues of the human hyaluronidase enzyme. This result showed good correlation with the earlier report (Zhou *et al.*, 2025). Similarly, two ligands (6, 6-Dimethoxy-octanoic acid, Methyl linoleate) has exhibited hydrogen bond interaction with ILE 73 amino acid residues of the target enzyme human hyaluronidase. This result is in excellent accordance with the previously published reports (Mancipe *et al.*, 2023; Xu *et al.*, 2024; Zhou *et al.*, 2025).

Similarly, in the present docking study, all the selected Dalethyne (DE) ligands have successfully docked with the human tyrosinase related protein 1. The swissdock binding energy ranges from the lowest Methyl nonanoate (-6.69 kcal/mol) to the highest Methyl octadec-8-enoate (-8.48 kcal/mol). More the negative value of the binding energy indicates more its affinity towards the target enzyme 3 (human tyrosinase related protein 1). The six chosen Dalethyne (DE) ligands have shown interactions with GLY 116 amino acid residues of Human Tyrosinase Related Protein 1 (hTYRP1) protein. This result showed good correlation with the earlier reports (Azimi *et al.*, 2025; Thong-Olran *et al.*, 2025). Similarly, two Dalethyne (DE) ligands (Dimethyl suberimidate, Tyrosol) exhibited hydrogen bond interaction with LYS 233 of hTYRP1 protein, which is in accordance to the previous reports (Azimi *et al.*, 2025; Thong-Olran *et al.*, 2025). On the other hand, two selected Dalethyne (DE) ligands (6,6-Dimethoxy-octanoic acid, Methyl 8,8-dimethoxyoctanoate) have displayed interactions with SER 106 amino acid residues of human tyrosinase related protein 1, which is on par with previously published report (Thong-Olran *et al.*, 2025). One chosen Dalethyne (DE) ligand (Methyl myristate) has shown hydrogen bond interactions with the SER 394 amino acid residue of hTYRP1. This result displayed

Table 4: Binding energy analysis of eighteen selected Dalethyne derivatives with human Tyrosinase Related Protein 1 (hTYRP1) using Swissdock web server.

Sl. No.	Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance H-A (A°)	Bond distance D-A (A°)	RMSD[a] compared with Tyrosol docked complex (A°)
1.	Dimethyl azelate	6.97	Gly 116 Tyr 226	2.04 3.29	2.95 3.90	0.45
2.	6,6-Dimethoxy-octanoic acid	7.11	Ser 106 Glu 451	3.32 1.84	3.68 2.78	0.58
3.	Dimethyl suberimidate	7.54	Cys 113 Gly 116 Lys 233 Gln 236	1.75 2.17 2.62 3.01	2.76 3.14 3.46 3.81	0.34
4.	Dimethyl undecanedioate	6.87	NI[b]	-	-	1.40
5.	Methyl arachidate	7.98	Gly 116	2.27	3.17	0.75
6.	Methyl behenate	8.11	NI[b]	-	-	0.40
7.	Methyl decanoate	6.88	Tyr 226	1.90	2.83	0.36
8.	Methyl 8,8-dimethoxyoctanoate	7.28	Ser 106 Gly 116	3.03 2.58	3.90 3.52	0.33
9.	Methyl 11-eicosenoate	7.60	NI[b]	-	-	2.10
10.	Methyl linoleate	8.24	NI[b]	-	-	0.46
11.	Methyl myristate	7.35	Ser 394	2.72	3.54	2.31
12.	Methyl nonanoate	6.69	Gln 236	3.57	4.03	0.28
13.	Methyl octadec-8-enoate	8.48	NI[b]	-	-	0.69
14.	Methyl 8-[(1s,2r)-2-octylcyclopropyl] octanoate	8.20	Gly 116	2.25	3.12	0.72
15.	Methyl oleate	8.44	NI[b]	-	-	0.63
16.	Methyl 9-oxononanoate	6.81	Arg 230	2.41, 2.99	3.16, 3.63	0.36
17.	Methyl palmitate	8.14	NI[b]	-	-	0.50
18.	Methyl stearate	8.46	NI[b]	-	-	0.41
19.	Oleocanthal	7.56	Gln 29 Cys 42 Asp 44 Arg 55 Asn 109	3.05 2.71 2.53, 1.93 2.61 3.37	3.70 3.63 3.45, 2.89 3.20 3.95	1.93
20.	Oleuropein	7.62	Arg 131 Glu 140 Ser 245 Glu 465	2.98 2.60 2.91 2.19	3.92 3.34 3.75 3.10	1.19
21.	Tyrosol	6.77	Cys 113 Gly 116 Lys 233 Leu 460	1.83 2.64 3.46 2.21	2.79 3.21 3.96 3.10	-

NOTE: RMSD[a]- Root mean square deviation, NI[b]-No hydrogen bond interactions.

good correlation with the earlier report (Veerichetty and Saravanabavan, 2023).

Moreover, two selected Dalethyne (DE) ligands (Dimethyl suberimidate, Methyl nonanoate) have exhibited interactions with GLN 236 amino acid residues of human tyrosinase related protein 1, which is on par with the previously published reports (Azimi *et al*., 2025; Thong-Olran *et al*., 2025). On the other hand, two chosen Dalethyne (DE) derivatives ligands (Dimethyl suberimidate, Tyrosol) have shown interactions with CYS 113 amino acid residues of hTYRP1 protein. This result is in accordance with the earlier report (Thong-Olran *et al*., 2025). One Dalethyne (DE) ligand (Oleuropein) has shown interactions with SER 245 amino acid residues of hTYRP1, which is on par with the previous reports (Azimi *et al*., 2025; Thong-Olran *et al*., 2025). One Dalethyne (DE) ligand (Methyl 9-oxononanoate) has shown hydrogen bond interactions with ARG 230 amino acid residues of human tyrosinase related protein 1 (hTYRP1). This result is in good correlation with the earlier report (Thong-Olran *et al*., 2025).

CONCLUSION

In the current investigation, the eighteen chosen Dalethyne (DE) ligands have shown the potential to dock with three enzymes (hNE, hHYAL and hTYRP1). However, three Dalethyne (DE) ligands (Methyl 11-eicosenoate, Methyl oleate and Methyl stearate) do not have shown any hydrogen bond interaction with any of the three target enzymes. Thus, the current findings provide new knowledge of these 18 selected Dalethyne (ligands) as potent (hNE, hHYAL and hTYRP1) modulating agents, which will help in managing good health and well-being, particularly cancer, inflammation, photo aging, pigmentation and wounds.

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ABBREVIATIONS

ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity; **BBB:** Blood-Brain Barrier Permeant; **CID:** Chemical Identification Number; **CYP1A2:** Cytochrome P450 family 1 subfamily A member 2 inhibitors; **CYP2C19:** Cytochrome P450 family 2 subfamily C member 19 inhibitors; **CYP2C9:** Cytochrome P450 family 2 subfamily C member 9 inhibitors; **CYP2D6:** Cytochrome P450 family 2 subfamily D member 6 inhibitors; **CYP3A4:** Cytochrome P450 family 3 subfamily A member 4 inhibitors; **DE:** Dalethyne; **GI:** Gastrointestinal absorption; **H:** High; **HT:** Hepatotoxicity; **hHyal:** Human hyaluronidase; **hNE:** Human Neutrophil Elastase; **hTYRP1:** Human tyrosinase-related protein 1; **IA:** Inactive; **L:** Low; **LCFA:** Long-Chain Fatty Acids; **N:** No; **ND:** Not determined; **NI:** No hydrogen bond interactions; **PDB:** Protein Data Bank; **P-gp:** P-glycoprotein substrate; **PLIP:** Protein-Ligand Interaction Profiler; **RMSD:** Root Mean Square Deviation; **ROS:** Reactive oxygen species; **3D:** Three-dimensional; **2D:** Two-dimensional; **VOO:** Virgin Olive Oil.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, **K.P., R.N.;** Methodology, **K.P., R.N.;** Software, **K.P., R.N.;** Formal analysis, **K.P., S.B.S., B.D., R.N.;** Investigation, **K.P., S.B.S., B.D., R.N.;** Resources, **K.P., R.N.;** Data curation, **K.P., S.B.S., B.D., R.N.;** Visualization, **K.P., S.B.S., B.D., R.N.;** Supervision, **R.N.;** Project administration, **K.P., R.N.;** Writing-original draft preparation, **K.P., S.B.S., B.D., R.N.;** Writing-review and editing, **K.P., S.B.S., B.D., R.N.;** All authors have read and agreed to the published version of the manuscript.

SUMMARY

In the current study, 18 chosen Dalethyne (ligands) were studied on the docking behaviour with three target enzymes (hNE, hHYAL and hTYRP1) by using the swissdock method. The docking analysis showed that Methyl stearate, Methyl arachidate and Methyl octadec-8-enoate has exhibited highest binding energy (-8.19, -8.51 and -8.48 kcal/mol) with hNE, hHYAL and hTYRP1 respectively.

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