RESEARCH PAPER

A Recent Review on Thymol-based Hybrids for the Treatment of Alzheimer's disease

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Received: 24th April, 2026; Revised: 20th May 2026; Accepted: 30th June, 2026; Available Online: 10th July, 2026

ABSTRACT
Amyloid-β (Aβ) plaque development, tau hyperphosphorylation, oxidative stress, neuroinflammation, metal dyshomeostasis, and cholinergic dysfunction are the causes of Alzheimer's disease (AD). It is progressive neurodegenerative illness that eventually results in cognitive decline and memory impairment. Although there are symptomatic medicines like cholinesterase inhibitors and NMDA receptor antagonists, there are still few effective disease-modifying drugs available. For the creation of multitarget-directed ligands (MTDLs), scaffolds based on natural products have drawn a lot of interest recently. The bioactive monoterpenoid phenol thymol (2-isopropyl-5-methylphenol) has become a promising pharmacophore among them due to its neuroprotective, reducing inflammation, antibacterial, and antioxidant activities. The design, synthesis, structure-activity relationship (SAR), and biological assessment of thymol-based hybrids for the treatment of AD are all covered in detail in this review. When compared to native thymol, structural alterations such carbamate, chalcone, triazole, benzamide, phenoxy acetamide, and other heterocyclic hybrids have far higher cholinesterase inhibitory action, and other activities were also incorporated. In conclusion, multifaceted pathophysiology of AD can be addressed by thymol-based hybrids, which are generally attractive multitarget therapy options. Active disease-altering drugs of Alzheimer's disease might be developed with further refinement and in vivo testing of these compounds.

Keywords: Alzheimer's disease, Thymol, Multi-directed ligands (MTDLs), AChE inhibitors, BuChE inhibitors, amyloid-β aggregation, Oxidative stress, neuroinflammation, Neuroprotection

How to cite this article: Sonali, Singh YP, Gaur A, Sharma R, A Recent Review on Thymol-based Hybrids for the Treatment of Alzheimer's disease. Int J Drug Deliv Technol. 2026;16(6): 1019-1033. DOI: 10.25258/ijddt.16.6.143
Source of support: Nil.
Conflict of interest: None

1. INTRODUCTION

The most frequent cause of dementia, accounting for 60% to 70% of cases, is Alzheimer's disease (AD), a neurodegenerative brain disorder associated with ageing that worsens over time. [1]The primary symptoms are usually problem in remembering recent events. As disease progresses, person experience confusion, memory loss, difficulty staying oriented, mood changes, and increasing problems with communication skills like speaking, writing, and reading.[2]Currently, more than 55 million people globally are living with AD, and, without new interventions, this number could rise to 152 million by 2050. In the United States alone, about 7 million people from the age of 65 to above have Alzheimer or dementia. It was one of the leading reasons of mortality in the U.S. in the same period when COVID-19 became one of the 10 most common causes of death. Interestingly, while deaths from heart disease, stroke, and HIV declined between 2000- 2021, deaths attributed to AD rise by more than 140% [3], [4].

Amyloid-beta (Aβ) and neurofibrillary tangles (NFTs) both within and outside of neurones are two harmful proteins that aggregate in AD. This aggregation of Aβ, and NFTs disrupts normal signalling between neuronal cells and eventually leads to their death. Although the exact cause AD is still not fully understood, but, important factors include damage to cholinergic neurons, accumulation of Aβ plaques, increased oxidative stress, abnormal changes in tau proteins, and imbalanced metal ions in the brain. Over the past three decades, researchers have proposed several theories to explain how these factors are involved in AD. In addition to protein aggregation, elevated metal levels and oxidative stress can increase the amount of harmful reactive oxygen species (ROS). These ROS disrupt the energy of cell production and further promote the formation of Aβ plaques and tangles, worsening the damage to brain cells [5].

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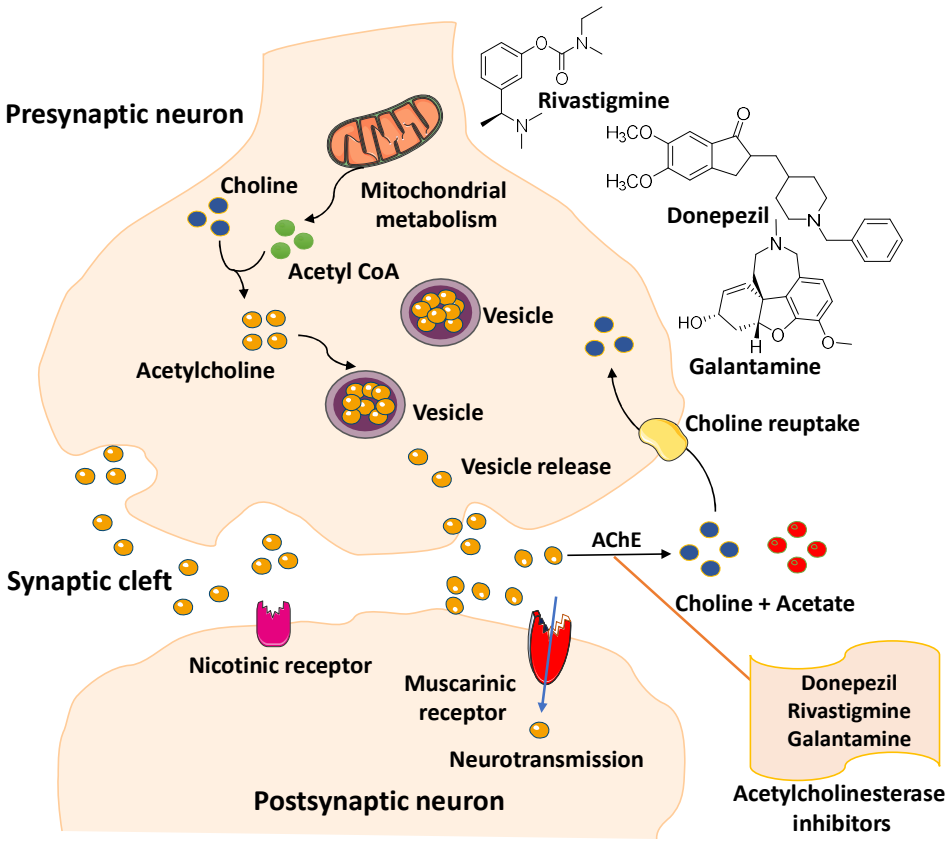


Figure 1. Pictorial representation of cholinergic neurotransmission in the synaptic cleft and its alterations associated with Alzheimer's disease (AD).

2. HYPOTHESIS OF ALZHEIMER'S DISEASE (AD)

AD is a typical brain disorder that gradually destroys nerve cells in both the inner and outer brain regions. Although its exact causes are not fully understood, but researchers have proposed several hypotheses, such as cholinergic, Amyloid cascade, metal ion, and oxidative stress hypothesis etc.

2.1 Cholinergic hypothesis

One of the first/oldest and most frequently known theories describing how AD develops is the cholinergic hypothesis, which was first proposed by Davies and Maloney in 1976. As per this hypothesis, acetylcholine (ACh) is the main neurotransmitter involved in the learning and memory. ACh normally uses the synaptic cleft to transfer signals from presynaptic to postsynaptic neurones. However, in AD, the amount of ACh decreases either because of decreased production or possibly because of increased hydrolysis by AChE, a crucial enzyme that cleaves ACh (**Figure 1**). Memory impairment results from neuronal cells' inability to communicate effectively when ACh levels fall. To maintain stable ACh levels and promote normal brain function in AD patients, medications that block AChE are employed [6].

2.2 Amyloid-β hypothesis

Amyloid beta (Aβ) is considered a major contributing factor in the progression of Alzheimer's disease (AD). The transmembrane protein amyloid precursor protein (APP) undergoes two distinct cleavage processes that produce Aβ. The first pathway, known as the amyloidogenic in which β (BACE1) and γ-secretase consecutively cut amyloid precursor protein by proteolysis and leads to the production of Aβ peptides, which are typically composed of 42 amino acids. Because of its hydrophobic C-terminal residues, $A\beta_{1\text{-}42}$ has a greater tendency to aggregate.[7] These peptides can self-associate, first producing soluble oligomers which are thought to be the most neurotoxic species and then aggregating into insoluble fibrils that deposit extracellularly as Aβ plaques. In contrast, α-secretase cleaves APP within the Aβ region in the non-amyloidogenic route, preventing the production of pathogenic peptides. This technique produces soluble APPα (sAPPα), a fragment having neuroprotective characteristics, as well as shorter non-amyloidogenic by-products. Therefore, a crucial factor in determining the health of neurones is the equilibrium between amyloidogenic and non-amyloidogenic pathways.[8], [9]

2.3 Tau hypothesis

Tau is a protein that is mostly present inside nerve cells, where it supports the movement of vital substances including proteins and neurotransmitters (such as dopamine and acetylcholine) and helps maintain the stability of the cellular structure. Under typical circumstances, tau is controlled by kinase and dynamically alternates between bound and unbound form of microtubule [10]. The cascade of tau aggregation is self-

replicating once it starts, exhausting the neuro's supply of functioning tau and turning it into harmful NFTs. Neuronal damage is the ultimate effect or this accumulation. As per aforementioned hypothesis these findings, the tau hypothesis is increasingly acknowledged as a viable target for the creation of AD medication candidates [7].

2.4 Oxidative stress hypothesis

According to the oxidative stress theory, an excessive buildup of reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), peroxide (O_2), hydroxyl radicals ($OH^{\bullet}$), and superoxide(O_2) damages key cellular components like the nucleus, mitochondria, and cytoplasm. Protein oxidation, damage to cell membranes, lipid degradation, and damage to DNA and RNA are some of the processes that cause this damage.[11] Reduced antioxidant function and toxicity are caused by overproduction of these species, which also damages DNA and RNA and causes protein oxidation, membrane damage, and lipid peroxidation. However, because AD involves numerous intricate and poorly understood biological mechanisms, developing effective treatments is difficult.[7]

2.5 Metal ion hypothesis

The metal ion hypothesis in AD revealed that the brain's dysregulation of iron, copper, and zinc increases the toxicity and aggregation of tau and β-amyloid (Aβ) proteins, which are key players in the pathophysiological of AD. According to studies, metal ions can cause oxidative neuronal damage and promote plaque development when they bind to Aβ, which can result in cognitive impairment. Therefore, regulating brain metal levels can lessen plaques and related toxicity, and molecular evidence suggests that detrimental protein aggregation can be almost completely eradicated with appropriate metal ion balance.

3. ALZHEIMER'S DISEASE (AD) TREATMENT CURRENTLY AVAILABLE

Currently available treatment for Alzheimer's are the cholinesterase antagonists [donepezil **(1)**, rivastigmine **(2)**, and galantamine **(3)**] and NMDA receptor inhibitor memantine **(4) (Figure 1)**. Nevertheless, these drugs simply relieve symptoms; it does not stop the disease's underlying progression. In year 2023-2024 anti-amyloid medicines lecanemab and donanemab have been developed, and these inhibit the aggregation of Aβ peptide. When used in the early stages of the illness, these therapies have been proven to be effective in eliminating Aβ plaques and decreasing cognitive deterioration by about 30%. Clinical trials often incorporate additional research methods that focus on tau pathology, neuroinflammation, and metabolic deficiencies [12].

4. MEDICINAL CHEMISTRY OF THYMOL

The main active ingredient in oil is thymol, a naturally occurring volatile monoterpenoid phenol that is extracted from a wide range of plants, including *Oliveris decumbens Vent, Ocimum gratissium L., Origanum L., Carum copticum L.,* and several types of *Satureja. Thymus vulgaris L*. is also commonly referred to as thyme. This multipurpose molecule has several real-world uses in fields including medicine, dentistry, veterinary care, food, and agrochemicals, to name few. Due to its potent cicatrising, antioxidant, antibacterial, and anti-inflammatory qualities its pharmaceutical uses have been the most studied and documented. The chemical name for thymol is 2-isopropyl-5-methylphenol (IPMP).[13]

4.1 Antioxidant activity

Thymol's antioxidant qualities have been systematically examined in several preclinical studies employing cell lines and animal models. The free radicals of hydroxyl were efficiently scavenged at elevated rates, resulting in the production of significant phenoxyl radicals are temporary species can be speed up by an alkaline media. The phenoxyl radical is produced upon dehydration when hydroxyl radicals are added to the phenolic group at its ortho position (C6 atom). The attack at the ortho position is more beneficial in terms of energy, however it is also anticipated that the assault at the para position will take place. Additionally, there is no precomplex development when additions are made at the ortho locations. A promising antioxidant moiety, thymol has a redox potential and is non-toxic.[14]

One of thymol's most well-researched effect is its capacity to scavenge free radicals by increasing the activity of superoxide and other naturally occurring antioxidant enzymes. The multifunctional and poly pharmacological characteristics of glutathione peroxide (GPx), glutathione-S-transferase (GST), catalase, vitamin C, vitamin E, reduced glutathione (GSH), and thymol dismutase (SOD) are examples of non-enzymatic antioxidants. Comparative studies have shown that thymol provides protection against oxidative damage to lipids and has superior reducing power, DPPH, superoxide, and hydroxyl radical scavenging capabilities. [15]

4.2 Anti-inflammatory activity

It has been shown that thymol (150μM) lessens the inflammation that LPS causes in mouse macrophage cell lines. Thymol (84μ/ml) treatment inhibited the messenger RNA expression of inducible nitric oxide (NO) in J774A.1 cell lines, thereby reducing macrophage inflammation produced by lipopolysaccharide (LPS) and interferon gamma (INF-γ) in-vitro. In human polymorphonuclear neutrophils (PMNs), thymol (10 and 20μg/ml) inhibited the release of elastase, a serine proteinase released by activated human neutrophils and a marker of inflammatory disease, in response to the synthetic chemotactic peptide N-formyl-methionyl-leucyl-phenylalanine (fMLP). Thymol (100μM) was reported to alter prostaglandin-catalysed synthesis by inhibiting both isoforms of cyclooxygenase (COX). With an IC5O of 0.2μM, it is especially potent against COX-1. These studies suggest that thymol may have anti-inflammatory qualities and can work similarly to non-steroidal anti-inflammatory drugs. In vitro, thymol (1.1μg/ml) prevented blood coagulation and platelet aggregation caused by arachidonic acid [14].

4.3 Antiparasitic agent

Thymol's pharmacological and bioactive potential effect make it one of the most significant phytochemical components. The alternative natural antiparasitic thymol, which may find application in the pharmaceutical sector, is the specific subject of this review. This is consistent with the need for safer, side-effect-free natural products for therapy. It has been discussed how thymol and carvacrol are biosynthesised as well as how thymol affects parasites. Thymol's study on the material confirmed its anti-parasite activities against anthelmintic, *Trypanosoma ssp., Toxoplasma gondii, Leishmania spp., Plasmodium falciparum, Giardia duodenalis, Eimeria spp., Cryptosporidium baileyi,* and *Cryptosporidium galli.*

Thyme and other plants that contain thymol have been used historically by various cultures as food spices and medicinal herbs. Due to great deal of research, their pharmacological qualities have been established, and a broad range of applications in various fields have been shown. The monoterpene nucleus's hydroxyl moiety on position C1 is thought to be responsible for the thymol molecule's action, despite its extremely simple structure. The assessment of thymol's extraction techniques, bioavailability, biological activity, potential adverse effects are all included in published research on the substance. Similarly, it is noteworthy that over the past five years, there have been an cumulative quantity of publications on the creation of novel comprising thymol, including biopolymers, metal nanospheres, nano emulsions, and dental resins that could be applied to food packaging, natural agrochemical, wounds, cavities, and disinfectants.[16]

5. THYMOL BASED HYBRIDS FOR THE TREATMENT OF ALZHEIMER'S DISEASE (AD)

In the year 2025 Zhang, Y.-L. et al. developed, and biologically assessed a new set of thymol-Carvacrol hybrids (**5a-5f**) (**Figure 2**) aimed at targeting extremely selective Anti-inflammatory BuCHE inhibitors [17].The enzyme assay revealed that most of the established compounds showed moderate to powerful BuChE inhibition activity. Compound **5c** exhibited the strongest BuCHE activity of all the synthesised compounds also tested significant effectiveness in improving the spatial remembrance of mice. In addition, to its strong anti-inflammatory and anti-BuCHE properties in vitro, **5c** was shown to be a promising multi-target candidate for the treatment of AD. It also showed far higher binding affinities to BuCHE than its parent compounds, carvacol and thymol. The crucial amino acid residues ASP70 and TYR332 formed hydrophobic interactions with the methyl and isopropyl groups of **5c**, which were found close to the PAS, according to the docking analysis. These results imply that **5c's** hydrophobic interactions with important amino acid residues that regulate enzyme activity are probably the cause of its increased anti-BuCHE activities. Additionally, the **5c** demonstrated anti-inflammatory properties at 10μM against BV2 cells production of IL1β in response to LPS. **5c** significantly repaired the scopolamine-induced memory deficit in the mouse mode in the *in vivo* behavioural testing, returning it to normal levels. This included decreasing latency, streamlining trajectory, and speeding up platform crossing times. The aforementioned findings showed that **5c** reduced the inflammatory response in AD rats while simultaneously improving memory deficits by restoring cholinergic function. All things considered, compound **5c** may represent a fresh avenue for the development of novel BuCHE inhibitors for the treatment of AD.

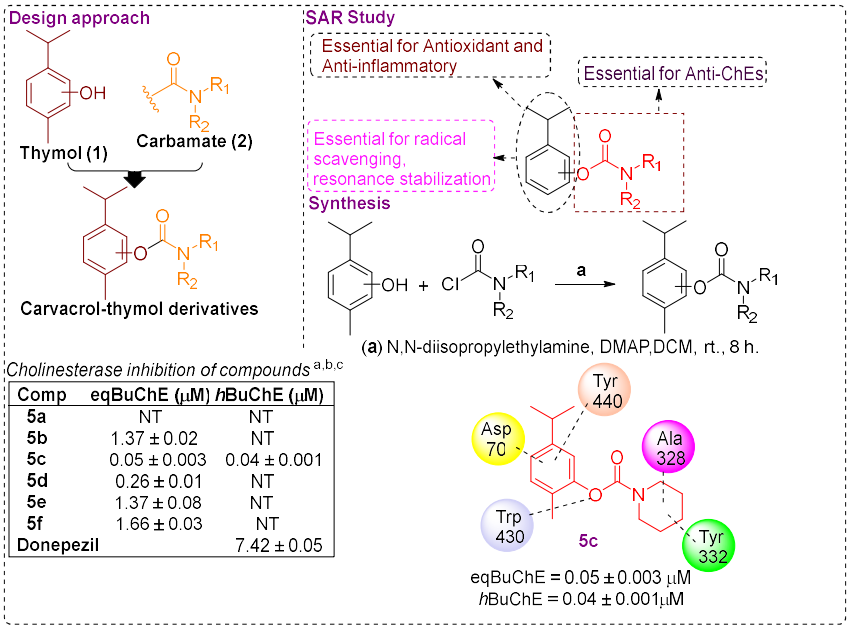
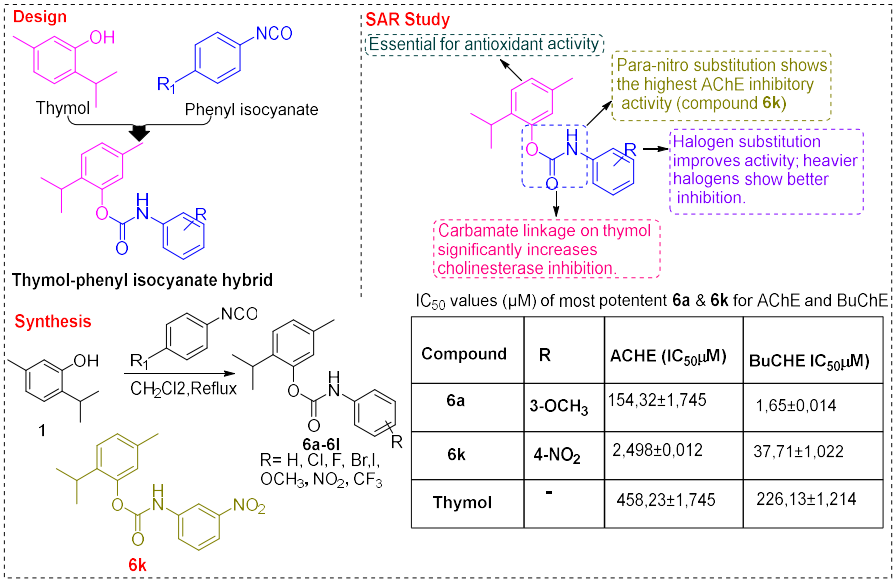


Figure 2. Design, SAR, biological activity and molecular docking study of Thymol-Carvacrol hybrid (**5a-5f**).

In (2017), Sonmez et al. created twelve new thymol-based carbamate derivatives in an effort to increase thymol's biological activity through structural alteration. Although thymol, a naturally occurring monoterpene, has a number of pharmacological characteristics, its native form exhibits relatively little cholinesterase inhibitory action. Thymol's

hydroxyl group was chemically altered by adding substituted phenyl carbamate moieties to increase its efficacy.

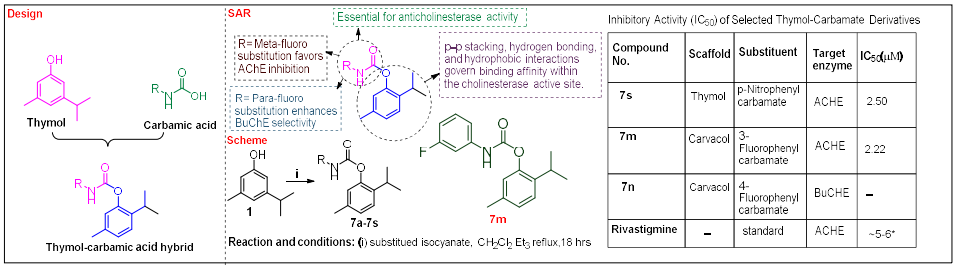
The type and location of substituents, such as halogen atoms, electron-donating and withdrawing groups, present on the phenyl ring differed among synthesised compounds **(6a–6l)**. The purpose of these modifications was to investigate how they affected the inhibition of enzymes. Comparing carbamate synthesis to the parent thymol molecule, biological analysis showed a substantial increase in inhibitory action. AChE was most strongly inhibited by compound **6k (figure 3)**, which contains a para-nitro substituted phenyl carbamate. This suggests that electron-withdrawing substituents at the para position are essential for increasing activity. The biological activity of thymol carbamates is significantly influenced by both electronic effects and substituent placement, as evidenced by the improved inhibition shown by other derivatives [18].



Compound	R	ACHE (IC_{50}μM)	BuCHE IC_{50}μM)
6a	3-OCH_3	154,32±1,745	1,65±0,014
6k	4-NO_2	2,498±0,012	37,71±1,022
Thymol	-	458,23±1,745	226,13±1,214

Figure 3. Design, SAR biological activity of Thymol-phenyl isocyanate hybrid **(6a-6l)**

Scaffolds generated from natural products, such carvacrol and thymol, have garnered interest for the creation of new anticholinesterase drugs. Two series of carbamate derivatives of thymol (**7a–8a**) and carvacrol (**7b–8b**) were synthesised by Kurt et al. (2017) utilising substituted aryl isocyanates in dichloromethane under reflux conditions with triethylamine (**Figure 4**). Using spectrum methods, the synthesised compounds were structurally characterised and their inhibitory effects against butyrylcholinesterase (BuChE) and AChE were assessed. To evaluate enzyme–ligand interactions and binding affinities, molecular docking and simulation experiments were also conducted. Outperforming common medications like galantamine and rivastigmine, the p-nitrophenyl-substituted molecule **7s** demonstrated strong AChE inhibition among the thymol derivatives of carbamate, having IC_{50} value of 2.50 μM. Likewise, 4-fluorophenyl analogue (**7m**) exhibited more BuChE inhibitory action, whilst the 3-fluorophenyl-substituted carvacrol carbamate (7s) indicated considerable AChE inhibition (IC_{50} = 2.22 μM). Steric effects, specifically the isopropyl group in thymol, which may affect enzyme binding, were cited as the reason for the differences in activity between thymol and carvacrol derivatives.[19].



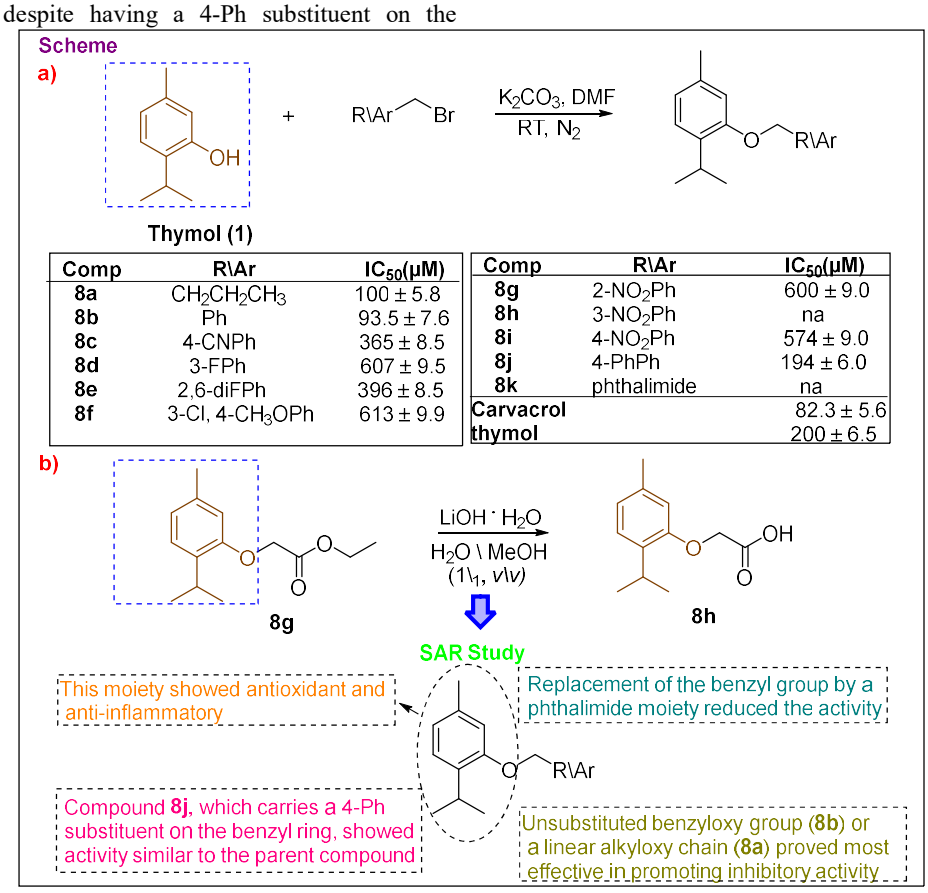
Compound No.	Scaffold	Substituent	Target enzyme	IC_{50}(μM)
7s	Thymol	p-Nitrophenyl carbamate	ACHE	2.50
7m	Carvacol	3-Fluorophenyl carbamate	ACHE	2.22
7n	Carvacol	4-Fluorophenyl carbamate	BuCHE	–
Rivastigmine	–	standard	ACHE	~5.6*

Figure 4: Design, SAR, and biological activity of thymol-carbamate hybrid **(7a-7s)**

6. MISCELLANEOUS HYBRIDS

In 2021, Sisto, F., and colleagues designed, synthesised, and evaluated thymol-based synthetic derivatives (**8a-8k**) (**Figure 5**) as inhibitor's dual-action in contradiction of various s H. pylori's strain and cell line of AGS [20]. The cytotoxic activity of a novel series of ether compounds based on the structure of thymol was tested against human gastric adenocarcinoma (AGS) cells, and the developed compounds were tested against eight strains of H. pylori. Only three of the **8a-8k** thymol derivatives **8a, 8b,** and **8j** showed a dose-dependent inhibitory effect on cell viability that was less effective than thymol. They all had IC50

values greater than 5-fluorouracil (5-FU, IC50= 82.3± 5.6 µM), the reference medication. All things considered, it was better to functionalise the OH moiety with either compound (**8b**) or (**8a**) in order to produce inhibitory activity below 100µM. The biological effect was diminished by substituting the benzyl ring with NO_2, F, or CN, as well as by poly-substitution of a phthalimide moiety (**8k**) for the benzyl group was likewise harmful. Remarkably, compound **8j** showed activity similar to the parent drug despite having a 4-Ph substituent on the benzyl ring. Because of its extremely high MLOGP value, compound **8j** also has a limited gastrointestinal absorption. Additionally, some derivatives may exhibit an antiproliferative action that is helpful in evaluating them as dual-acting medicines to prevent the development of stomach cancer. The potential of these compounds to treat biofilm-associated *H.pylori* infections *in vitro* and *in vivo* will be investigated further because of their parent compound's capacity to disaggregate.[21]



Comp	R\Ar	IC_{50}(µM)
8a	$CH_2CH_2CH_3$	100 ± 5.8
8b	Ph	93.5 ± 7.6
8c	4-CNPh	365 ± 8.5
8d	3-FPh	607 ± 9.5
8e	2,6-diFPh	396 ± 8.5
8f	3-Cl, 4-CH_3OPh	613 ± 9.9

Comp	R\Ar	IC_{50}(µM)
8g	2-NO_2Ph	600 ± 9.0
8h	3-NO_2Ph	na
8i	4-NO_2Ph	574 ± 9.0
8j	4-PhPh	194 ± 6.0
8k	phthalimide	na
Carvacrol		82.3 ± 5.6
thymol		200 ± 6.5

Figure 5. design, development, (SAR), and docking study of various hybrids (**8a-8k**).

In the 2024, Shahi, A., et al., intented and developed, and antibacterial potential of new sequence of dihydropyrimidinone and dihydropyridine derivatives (**9a-9d**) (**Figure 6**) of thymol contrary to methicillin-resistant *Staphylococcus aureus* and *P. aeruginosa* pathogenic microorganisms [22]. Nine thymol derivatives were completely synthesised, and their antibacterial properties were tested against both Gram-positive and Gram-negative organism, including MRSA and *P. aeruginosa*. With MIC values of 12.5µM for *P. aeruginosa* and 50.0µM for MRSA, compound **9d** demonstrated strong action against both bacteria. Thymol (**1**) was extracted from Jammu Monarda and used to create thymol aldehyde (**3**) (Scheme 1). Additionally, a modification of these compounds with derivatives of pyrimidinone and pyridine is disclosed. (Scheme 2)

Among all the synthesised compounds, compound **9d** shown notable antibacterial activity against MRSA and *P.aeruginosa.* With MIC values ranging from 12.5 to 50.0µM, compound **9d** suppressed the development of both MRSA and *P.aeruginosa.* The remaining derivatives showed antibacterial efficacy as well, although only at higher concentrations (>100µM) against broad-spectrum pathogens as *M. smegmatis, K. pneumoniae,* and *E. coli.* The study also contained standard positive control vancomycin, which had MIC values of 6.25 and 3.1 µM against MRSA and *P. aeruginosa*, respectively. Using vancomycin as the standard, the antibacterial activity of thymol and its derivative **9d** against *P. aeruginosa* (Gram-negative) and MRSA (methicillin-resistant *S. aureus*) (Gram-positive) bacterial strains shown good efficacy against clinically isolated bacterial strains. Thymol (**1**) exhibits a binding affinity (docking score -5.2kcal/mol) to the protein interaction, while compound **9d** has a greater binding affinity (docking score -6.9 kcal/mol). Docking chemical **9d** clearly amino acids, such as Tyr249, Pro241, Val151, and Pro148 through normal hydrogen bonds,

Pro243 through pi-alkyl bonds, and Asp149 through pi-sigma bonds. Compared to the parent chemical (thymol), compound **9d** showed superior hydrogen bonding interaction with the protein.

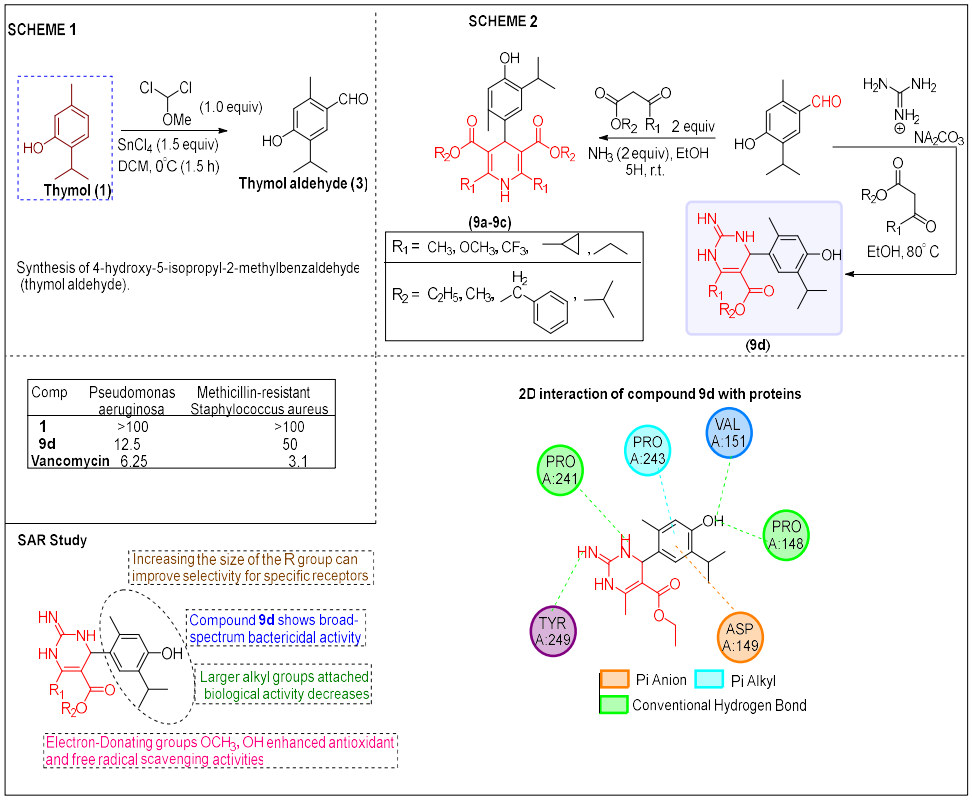


Figure 6. Design, synthesis, and (SAR) study of miscellaneous derivatives (**9a-9d**).

In 2009 Sathe, P.S., et al. developed a diverse series using a green synthesis method, novel benzamide compounds (**10a-10c**) that share strutural similarities with paracetamol were created from thymol in this **figure 7**[23]. They totally synthesized 5 compounds, tested them against antioxidant and antibacterial properties. These derivatives were tested for antioxidants using the DPPH assay and for antibacterial activity against five microbes. Synthesising paracetamol analogues from thymol is the goal of the study described here. Solvent-free synthesis of these derivatives produces high-quality products quickly. The contact with several amino acid residues of human heme oxygnase-1 is essential for their antioxidant activity, according to their docking studies against the active site of the enzyme. Thymol (**1**) was first treated with sodium nitrite and concentrated HCl at 0°C to produce the intermediate 4-nitrosothymol (**4**). 4-aminothymol (**5**) was then created by reacting this intermediate with ammonia and hydrogen sulphide at room temperature. Ultimately, 4-aminothymol was reacted with different benzoyl chlorides at ambient temperature in a solvent-free (neat) environment to produce the desired compounds (**10a-10c**). the final products were crystallised from ethanol in order to purify them. All of the substance were shown to have good to moderate DPPH radical scavenging activity. Such antioxidant activity may be caused by the benzamide's free phenolic -OH and -NH, -C=O groups [24].

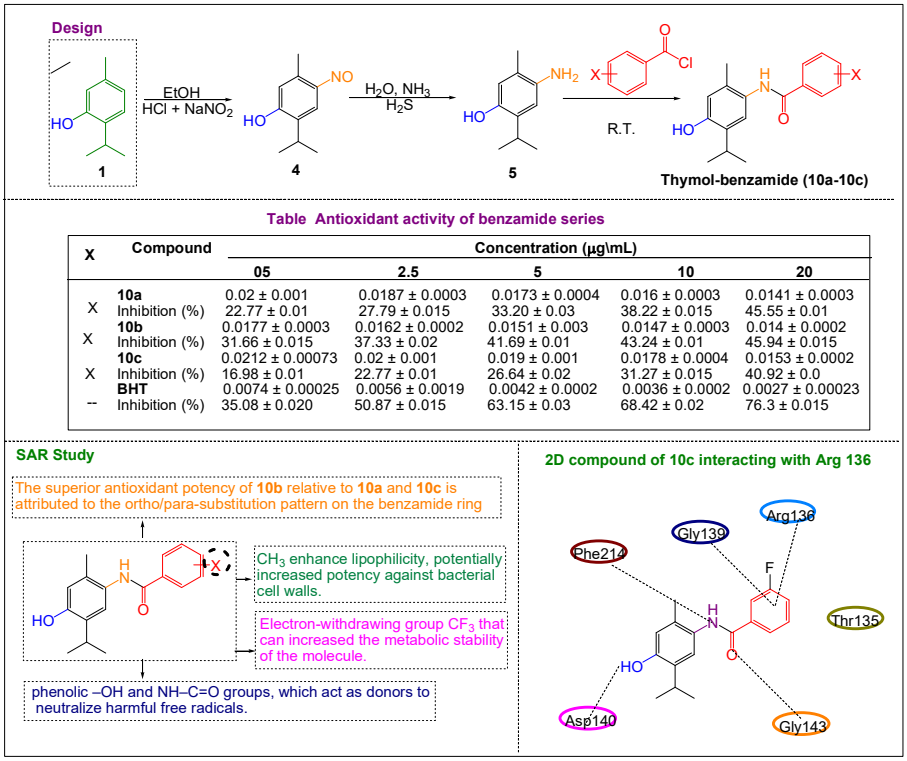


Table Antioxidant activity of benzamide series

X	Compound	Concentration (µg\mL)				
		05	2.5	5	10	20
X	**10a**	0.02 ± 0.001	0.0187 ± 0.0003	0.0173 ± 0.0004	0.016 ± 0.0003	0.0141 ± 0.0003
	Inhibition (%)	22.77 ± 0.01	27.79 ± 0.015	33.20 ± 0.03	38.22 ± 0.015	45.55 ± 0.01
X	**10b**	0.0177 ± 0.0003	0.0162 ± 0.0002	0.0151 ± 0.003	0.0147 ± 0.0003	0.014 ± 0.0002
	Inhibition (%)	31.66 ± 0.015	37.33 ± 0.02	41.69 ± 0.01	43.24 ± 0.01	45.94 ± 0.015
X	**10c**	0.0212 ± 0.00073	0.02 ± 0.001	0.019 ± 0.001	0.0178 ± 0.0004	0.0153 ± 0.0002
	Inhibition (%)	16.98 ± 0.01	22.77 ± 0.01	26.64 ± 0.02	31.27 ± 0.015	40.92 ± 0.0
--	**BHT**	0.0074 ± 0.00025	0.0056 ± 0.0019	0.0042 ± 0.0002	0.0036 ± 0.0002	0.0027 ± 0.00023
	Inhibition (%)	35.08 ± 0.020	50.87 ± 0.015	63.15 ± 0.03	68.42 ± 0.02	76.3 ± 0.015

Figure 7. development, (SAR) study, and molecular docking study of miscellaneous derivatives (**10a-10c**).

In 2025, Kumari, A.et.al. designed, Synthesis and computational analysis of novel chalcones generated from thymol and their hybrids with benzotriazoles (**11a-11c** and **12a-12c**) as antimicrobial agents [25]. FTIR, ^{1}H NMR, ^{13}C NMR and HRMS spectrum methods were used to characterise the 10 compounds that were synthesised. Software tools evaluated drug-likeness characteristics, molecular docking, ligand-receptor complex binding energies, ADMET, and similarity for test compounds. With MIC values of 12.91 and 14.72µg/ml, respectively, **12a** and **12b** showed the most potency of all against *C. albicans* and *C. mycoderma.* Several molecular hybrids were developed, synthesised, and evaluated for computational and antibacterial characteristics in this work. In this study, hybrids were created and their antibacterial activity was assessed using *in vitro* experiments.

The matching thymol-chalcone hybrids were obtained by synthesising thymol (**1**), 1-bromo-3-chloropropane (**6**), para-aminoacetophenone (**7**), and a substituted benzaldehyde (**8**). For lanosterol α-demethylase and DNA gyrase topoisomerase B (**11a-11c**), compounds (**12a-12c**) shown good efficacy in the docking study. The majority of the compounds, particularly **11a**, had strong amoxicillin similarities, whereas **12a** showed impressive fluconazole effects. While compounds **12a** and **12b** showed significant potency against *C. albicans* and *C. mycoderma* with MIC values of 12.91 and 14.72 µg/ml, respectively, compound **11a** showed excellent potency against *S. aureus* and *E. coli* with MIC values of 12.16 µg/ml and 13.5 µg/ml respectively. Additionally, the thymol-derived chalcones (**11a, 12a, 12b**) have demonstrated strong antifungal and antibacterial action. Chalcone **11a** reacted with benzotriazoles **12a, 12b,** and **12c** to produce further benzotriazole analogues. The test substances yielded a good proportion (78-51%). The antibacterial activity of synthesised compounds is enhanced by electron-donating groups (-OCH_3, -CH_3), but the antifungal activity is increased by electron-withdrawing groups (-Cl, benzotriazole), according to SAR data. Overall, the study indicates that compounds **11a** and **12a**, which are the most active, could serve as lead compounds for the development of more antimicrobial compounds.

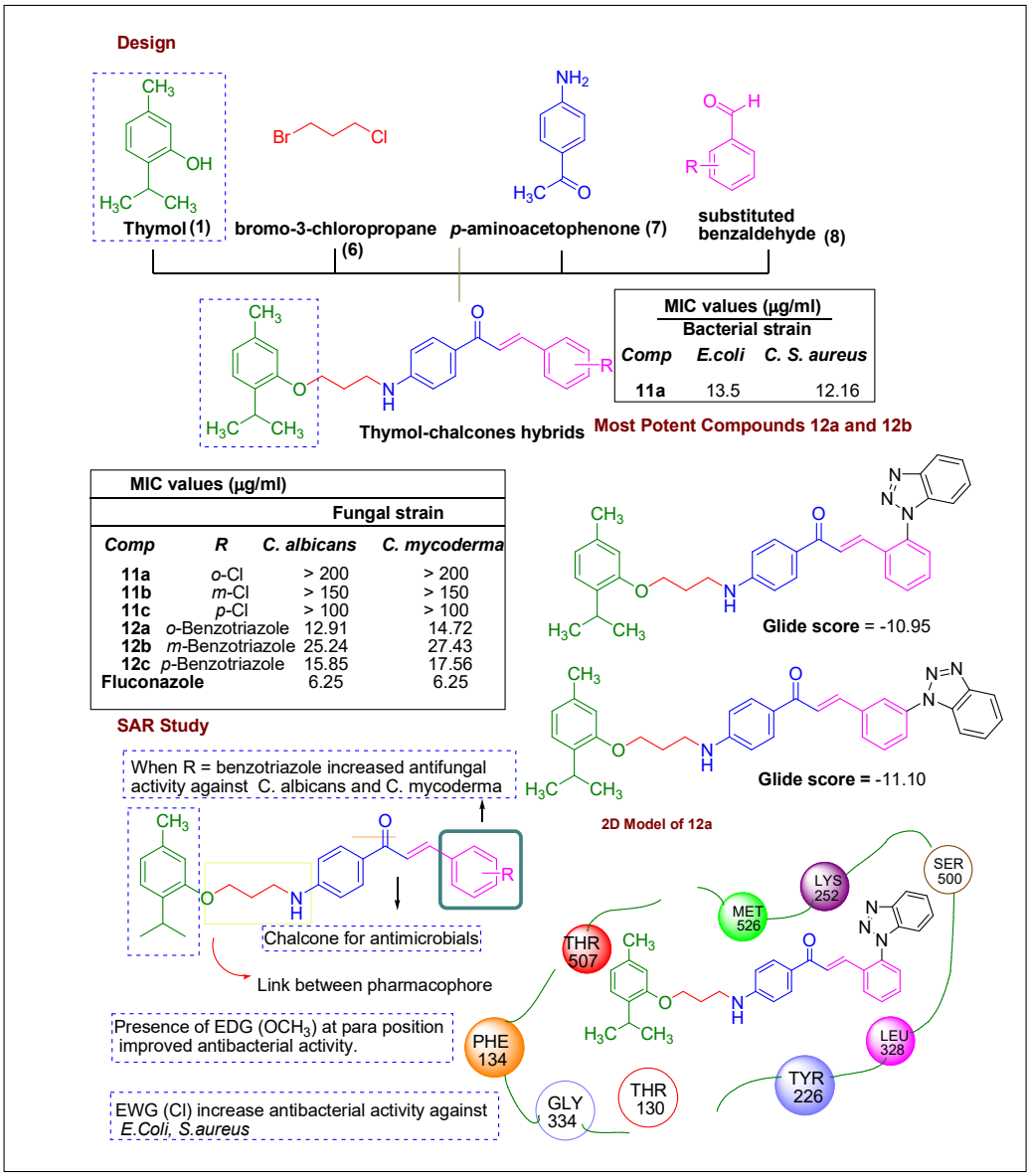
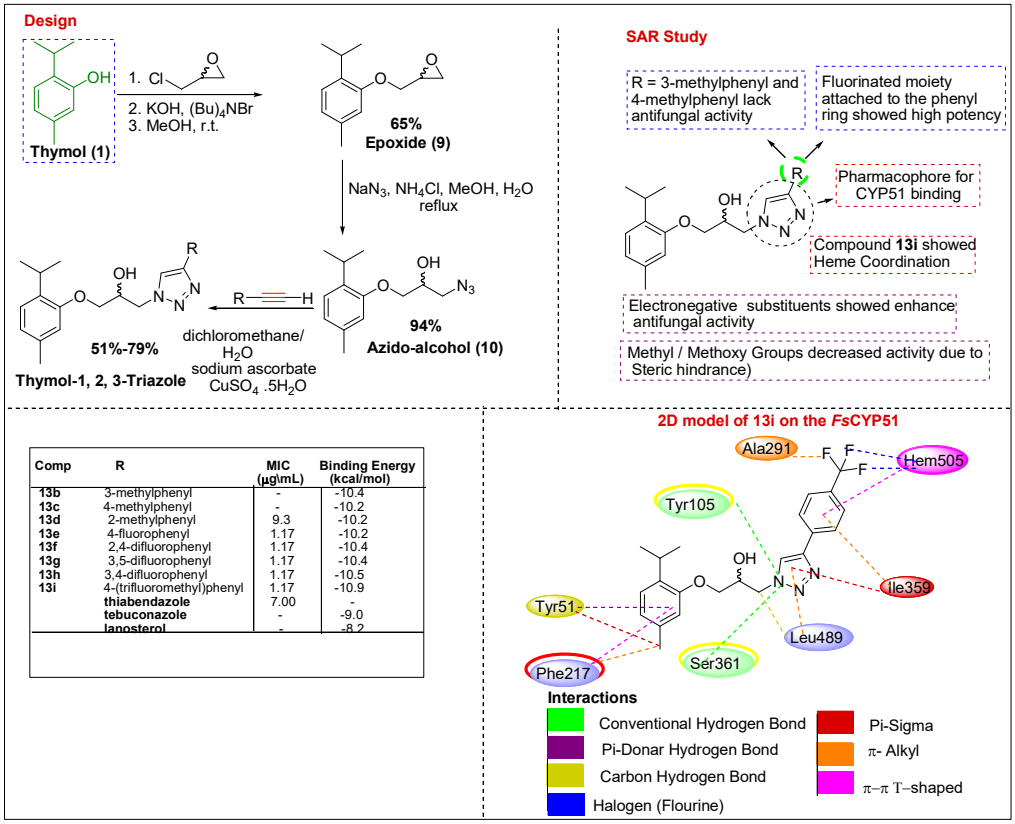


Figure 8. Design, (SAR) study and molecular docking study of miscellaneous thymol-derived chalcones and their benzotriazoles hybrids (**11a-11c** and **12a-12c**).

In the year 2025, de Oliveira, M.B., et al. creation and production of thymol derivatives (**13a-13i**) with a 1,2,3-triazole moiety to protect papaya from *Fusarium solani*[26]. They totally synthesized twenty compounds integrating a moiety containing 1,2,3-triazole was produced in three steps, the most important of which is the azide-alkyne cycloaddition (CuAAC) reaction catalysed by copper(I) [27], [28]. The range of growth inhibition was 1.17 to 37.5µg/ml; compounds **13e, 13f, 13g, 13h,** and **13i** showed the lowest values (1.17µg/ml). when it came to *F. solani,* compounds with phenyl rings and electron-donating groups (methyl or methoxy) frequently showed no effect. Interestingly, the most active pf these derivatives are fluorinated compounds **13e, 13f, 13g, 13h,** and **13i**, which have shown promise as antifungal research candidates with potential uses in both agriculture and medicine. Interestingly, derivatives **13e**, **13f**, **13g**, **13h**, and **13i** showed a strong affinity for *Fs*CYP51, the corresponding binding energies of -10.2, -10.4, 10.5, and -10.9 kcal/mol. Although the derivatives **13b** and **13c** lack antifungal activity (**figure 8**), they exhibited favourable interactions with CYP51 active also due to steric effects, a methyl or methoxy group in the phenyl moiety may or event them from reaching the active site. Overall, it was demonstrated that the derivatives interact with a rather consistent set of CYP51 residues. When it comes to mediating interactions with thymol derivatives, these residues are crucial. It's interesting to note that only compound 13i interacts directly with the heme cofactor; the other derivatives are situated around 5 Å away from the iron atom in the heme group. Significant effects were displayed by the five most active substances, with a

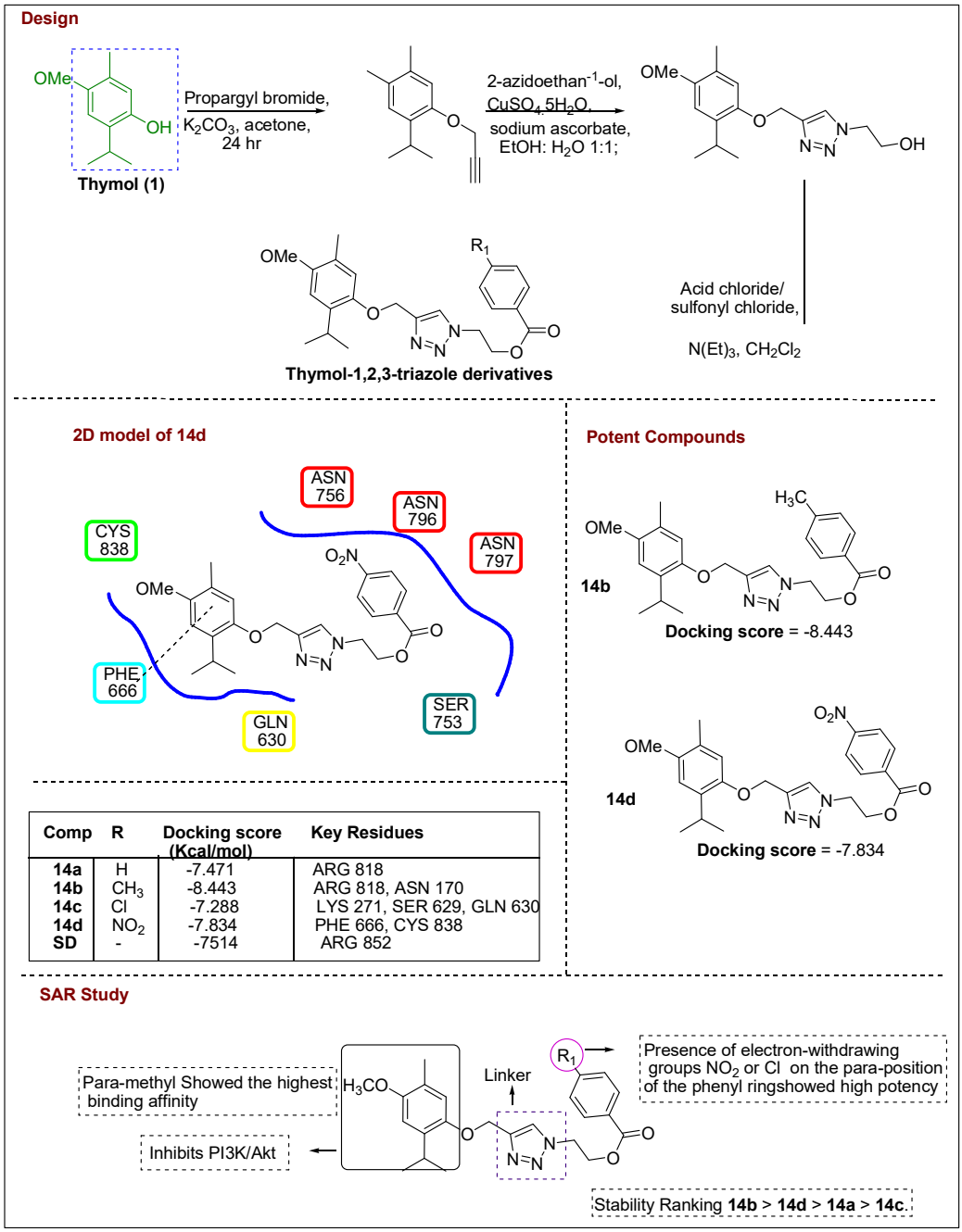
minimum inhibitory concentration (MIC) of 1.17 µg/mL, according to an evaluation of their antifungal activity. Many potent compounds have a structural feature: a fluorine atom or fluorinated moiety attached to the phenyl ring connected to the 1,2,3-triazole ring. The overall findings indicate that the synthesised compounds may offer promising alternatives for the development of new antifungal drugs for the control of *F. solani* in papaya crops.



Comp	R	MIC (µg\mL)	Binding Energy (kcal/mol)
13b	3-methylphenyl	-	-10.4
13c	4-methylphenyl	-	-10.2
13d	2-methylphenyl	9.3	-10.2
13e	4-fluorophenyl	1.17	-10.2
13f	2,4-difluorophenyl	1.17	-10.4
13g	3,5-difluorophenyl	1.17	-10.4
13h	3,4-difluorophenyl	1.17	-10.5
13i	4-(trifluoromethyl)phenyl	1.17	-10.9
	thiabendazole	7.00	-
	tebuconazole	-	-9.0
	lanosterol	-	-8.2

Figure 9 Design, (SAR) study and molecular docking study of miscellaneous thymol-derived Thymol-1, 2, 3-Triazole hybrids (**13a-13i**).

A unique set of Thmol-1,2,3-triazole derivatives (**14a-14d**) were created and synthesised by Laamari, Y. et a. in 2024 as possible treatments for breast cancer [29]. Nine chemicals were synthesised in order to target breast cancer. In the PI3K-Akt signalling system, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) is essential for breast cancer cell growth, survival, and proliferation. Compound **14a** exhibited hydrophobic interaction with ARG 818, while compound **14b** shown both hydrophobic interaction with ARG 818 and Arene-H bond with ASN 170. Compound **14c** interacted hydrophobically with GLN 630 after forming an Arene-H bond with LYS 271 and SER 629, while compound **14d** interacted hydrophobically with CYS 838 and created an Arene-Arene link with PHE 666. Complex **14b** exhibits outstanding stability, with a maximum RMSD of 2.0 Å and an average RMSD of 1.0 Å. Compound **14b** complex shows amazing stability throughout the simulation, with a maximum RMSD of 3.2 Å and an average deviance of 1.4 Å. Even though complex **14b** exhibits some instability at the beginning of the simulation, it eventually stabilises within the 3 Å permissible deviation range. Compound **14b** (*p*-methyl) and (*p*-nitro) had the best docking scores, according to in-silico molecular docking experiments, with low energy conformations of 8.4 kcal/mol and 7.8 kcal/mol, respectively, and strong contacts between ARG 818 and ASN 170 residues. According to overall study, compounds **14b** and **14d** can be regarded as viable candidates targeting breast cancer since they consistently showed structural stability in ligand-protein complexes over the course of the 100 ns simulation.



Comp	R	Docking score (Kcal/mol)	Key Residues
14a	H	-7.471	ARG 818
14b	CH_3	-8.443	ARG 818, ASN 170
14c	Cl	-7.288	LYS 271, SER 629, GLN 630
14d	NO_2	-7.834	PHE 666, CYS 838
SD	-	-7514	ARG 852

Figure 10 Design, (SAR) study and molecular docking study of miscellaneous thymol-derived Thymol-1, 2, 3-Triazole hybrid (**14a-14d**).

In the year 2025 R. Rabee, A. and colleagues designed, synthesized and characterized thymol-phenoxy acetamide derivatives (**15a-15b**) and (**16a-16b**) aimed at targeting parasitological investigation [30]. Compounds **15a**, **15b**, **16a**, and **16b** demonstrated high gastrointestinal absorption and permeability in Blood Brain Barrier (BBB) was noticed just in **15a** and **16a**. Cytochrome P450 enzymes were shown to be selectively inhibited; compound **16b** inhibited CYP1A2, while compounds **15a**, **16a**, and **16b** inhibited CYP2C19. Because of their high GI absorption, moderate solubility (ESOL log S of -4.24, -5.46, -5.11), balanced lipophilicity (consensus; log Po/w 2.95,3.91, 3.39), and TPSA (75.71,77.4, 103.42 ± 2), compounds **15a, 16a,** and **16b** were the most promising. They produced an improved therapeutic safety profile by specifically inhibiting CYP2C19 and CYP2C9 and without interacting with CYP1A2, CYP2D6, or P-gp. However, compound **16b** stands out as a preferred possibility because of it lack in permeability of Blood Brain Barrier, that may decrease potential negative effects on the central nervous system. Compound **15a** formed hydrogen bonds with important catalytic residues which is

very high, demonstrating a high binding of -7.42kcal/mol. Asp219, Met136, and Lys105, along with stablishing π-alkyl and Vander Waals interactions, highlight its potential as a inhibitor. Compound **15b** interacted with Asp219, Lys105, and Phe220 and had the second-highest binding affinity (-6.45 kcal/mol), indicating a somewhat weaker but still significant binding configuration. Compound **16b** displayed a similar binding affinity (-6.41 kcal/mol), suggesting a stable binding profile, with typical hydrogen bond interactions involving Tyr155 and Aspp219. Compound **16a** demonstrated a lower binding affinity (-5.39 kcal/mol), suggesting a less stable binding mechanism, with limited hydrogen bond interactions involving Asp219. Despite having a slightly lower binding affinity than compounds **15a** and **15b,** compound **16b** demonstrated the highest *in vivo* antiparasitic efficacy. Its balanced ADMET profile, which included selective cytochrome P450 inhibition, intermediate solubility, and high GI absorption, enhanced its efficacy and bioavailability. Compound **15a, 15b,** and **16b** are promising possibilities for the creation of effective antiparasitic medications, according to the overall study's findings.

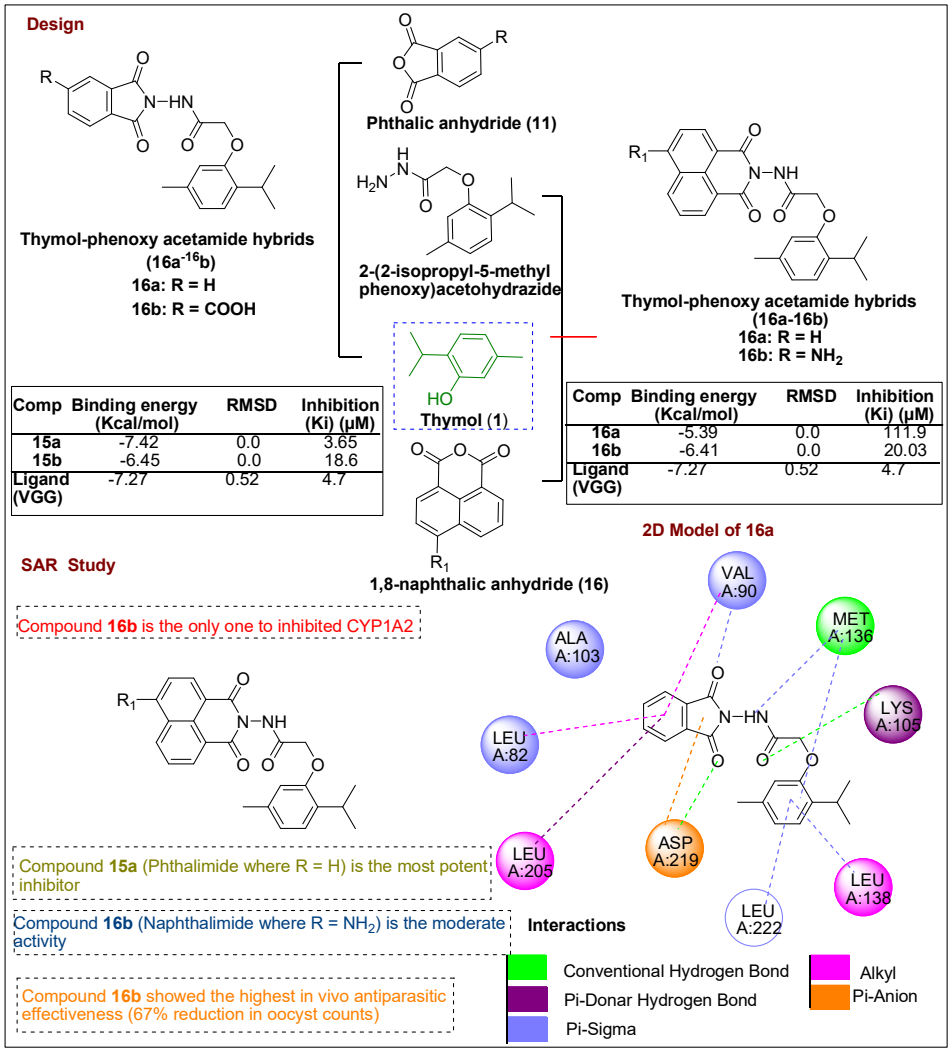
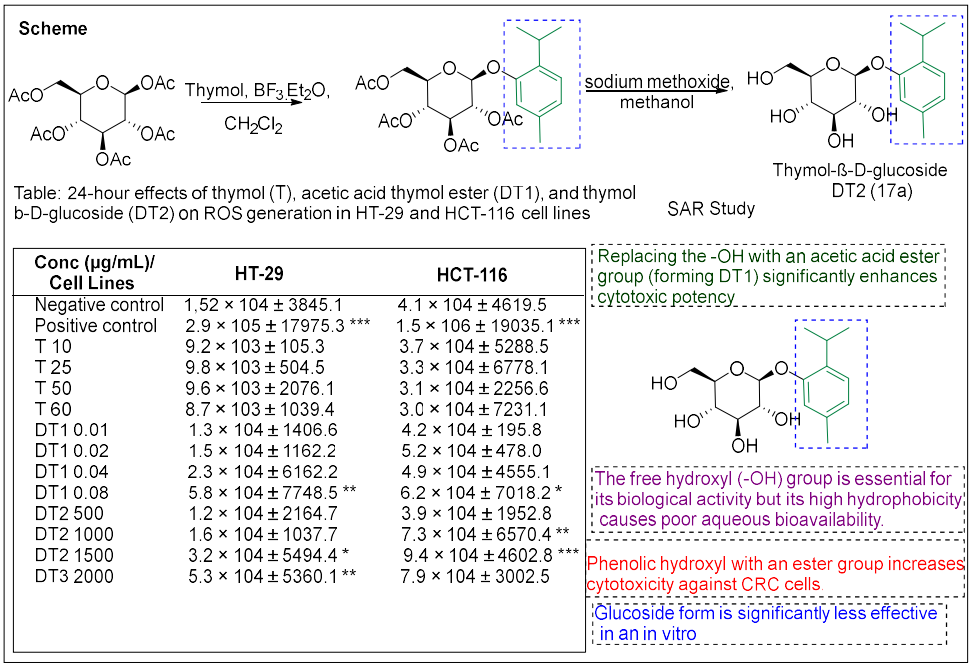


Figure 11 Design, (SAR) study and molecular docking study of miscellaneous thymol-phenoxy acetamide hybrids (**15a-15b** and **16a-16c**).

A new set of thymol derivatives (acetic acid thymol ester, (DT1) thymol β-D-glucoside (DT2) (**17a**) were created in 2022 by Blaňčková, M. et al. in relation to their hydrophilic properties and their impact on colorectal cancer.[31] Figure 10 illustrates how the MTT assay was used to evaluate the cytotoxic effect of the novel compounds on the colorectal cancer cell lines HT-29 and HCT-116. They biologically evaluated how these compounds affected the colorectal cancer cell lines HT-29 and HCT-116. We identified the impacts on cell proliferation, micronucleus formation, ROS production, and cytotoxic and genotoxic effects. Derivatives of thymol may offer a more successful strategy for colon cancer treatment and prevention. Using the ROS- GloTM H_2O_2 Assay, the impact of the investigated chemical on ROS production was assessed at various concentrations (10-60μg/ml for T, 0.01-0.08μg/ml for DT1, and 500-2000μg/ml for DT2) in HT-29 and HCT-116 cells (**17a**).

The data show that DT1 raised the luminescence intensity in the HT-29 cell libe by 0.08µg/ml (~380%), although HCT-116 cells only produced 151% more ROS than the untreated control cells. Cells were indeed subjected to cytotoxic and genotoxic effects at these doses. At a dose of 1500µg/ml, derivative DT2 dramatically raised ROS production by over 210% for both cell lines. In contrast to the untreated control cells, DT2 (**17a**) enhanced ROS production by 349% for the HCT-116 cells at the maximum dose. Because to cytotoxicity, there are less cells which accounts for the difference in value. The investigated cell lines showed no increase in ROS when exposed to thymol Acetic acid thymol ester, a thymol derivative, generally exhibited cyto/genotoxic effects and generated ROS at far lower doses (~0.08µg/ml) than the standard (~60µg/ml). this supported the theory that the derivatives hydrophilic qualities could work more potently and be used to cure or prevent colorectal cancer.



Conc (µg/mL)/ Cell Lines	HT-29	HCT-116
Negative control	1.52 × 104 ± 3845.1	4.1 × 104 ± 4619.5
Positive control	2.9 × 105 ± 17975.3 ***	1.5 × 106 ± 19035.1 ***
T 10	9.2 × 103 ± 105.3	3.7 × 104 ± 5288.5
T 25	9.8 × 103 ± 504.5	3.3 × 104 ± 6778.1
T 50	9.6 × 103 ± 2076.1	3.1 × 104 ± 2256.6
T 60	8.7 × 103 ± 1039.4	3.0 × 104 ± 7231.1
DT1 0.01	1.3 × 104 ± 1406.6	4.2 × 104 ± 195.8
DT1 0.02	1.5 × 104 ± 1162.2	5.2 × 104 ± 478.0
DT1 0.04	2.3 × 104 ± 6162.2	4.9 × 104 ± 4555.1
DT1 0.08	5.8 × 104 ± 7748.5 **	6.2 × 104 ± 7018.2 *
DT2 500	1.2 × 104 ± 2164.7	3.9 × 104 ± 1952.8
DT2 1000	1.6 × 104 ± 1037.7	7.3 × 104 ± 6570.4 **
DT2 1500	3.2 × 104 ± 5494.4 *	9.4 × 104 ± 4602.8 ***
DT3 2000	5.3 × 104 ± 5360.1 **	7.9 × 104 ± 3002.5

Figure 12 Synthesis and structure-activity relationship (SAR), of derivatives of thymol (acetic acid thymol ester, thymol β-D-glucoside) compound (**17**).

6. CONCLUSION

Thymol-based hybrids, which combine antioxidant, cholinesterase inhibitory, and anti-amyloid properties, have become promising multitarget medicines for Alzheimer's disease. Metal-coordinated derivatives, carbamate, tacrine, coumarin, carbazole, and triazole are examples of these hybrids. They target important AD disease include metal dyshomeostasis, oxidative stress, amyloid-β aggregation, and cholinergic dysfunction. Studies of the structure-activity relationship show that their biological potency and selectivity are significantly influenced by metal coordination, spacer length, and functional groups. In preclinical models, these multitarget hybrids show enhanced neuroprotective efficacy and serve as important starting points for future drug development aimed at disease-modifying Alzheimer's treatments.

Acknowledgement

Sonali sincerely acknowledges Chandigarh University for granting a fellowship to support his postgraduate project work.

Conflicts of interest statement

The author declares no conflicts of interest.

Data availability statement

Research data are not shared

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