



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Research Article

In-Silico Drug Design and Molecular Docking Studies of Some Novel Thiophene Derivatives Targeting Pde4d Inhibitors as Chronic Obstructive Pulmonary Disease Agents

Neelambari S.*, Priyadharshini R., Mohammed Idrees H., Jawaharsamuvel R.

College of Pharmacy, Madras Medical College, affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India.

ARTICLE INFO

Published: 07 Jan. 2025

Keywords:

In-silico drug design,
Molecular docking,
Thiophene derivatives,
PDE4D inhibitors, COPD
therapy, ADMET analysis.

DOI:

10.5281/zenodo.14609519

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by airflow limitation and inflammation. Phosphodiesterase 4D (PDE4D) inhibitors have emerged as promising therapeutic targets for COPD due to their ability to modulate cyclic AMP levels and reduce inflammation. In this study, an in-silico approach was employed to design and evaluate novel thiophene derivatives as potential PDE4D inhibitors. Molecular docking studies were conducted to predict the binding interactions of these derivatives within the active site of PDE4D. The docking results revealed strong binding affinities, indicating that these compounds could effectively inhibit PDE4D activity. The key interactions between the ligands and the amino acid residues within the PDE4D binding pocket were analysed to understand the structure-activity relationships (SAR). Furthermore, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling ensured that the designed derivatives possess favourable pharmacokinetic properties. This study highlights the potential of thiophene derivatives as lead compounds for the development of new COPD therapies.


INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory condition characterized by persistent airflow limitation and an inflammatory response in the lungs. It is a significant cause of morbidity and mortality

worldwide, impacting the quality of life of millions of individuals and posing a substantial economic burden. ^[1] COPD develops gradually and is often diagnosed in middle-aged or older adults with a history of smoking or prolonged exposure to irritants. The disease progresses over

***Corresponding Author:** Neelambari S.

Address: College of Pharmacy, Madras Medical College, affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India.

Email : neelusms99@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



time, with symptoms becoming more severe and leading to complications like respiratory failure, cardiovascular issues, and increased susceptibility to lung infections. Despite being preventable and treatable, COPD remains a leading cause of death globally due to underdiagnosis and late intervention. ^[1,3] Chronic Obstructive Pulmonary Disease (COPD) encompasses two primary conditions, often coexisting, that contribute to breathing difficulties:

1. Chronic Bronchitis

- Characterized by long-term inflammation of the bronchial tubes (airways).
- Leads to excessive mucus production, coughing, and frequent respiratory infections.
- Patients typically experience persistent cough (often called “smoker’s cough”) and mucus expectoration.

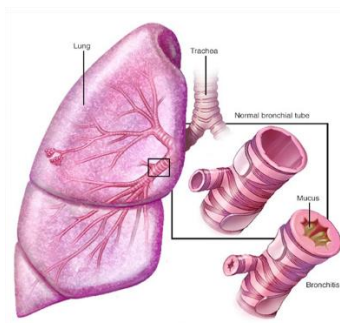


Figure No.1: Chronic Bronchitis

2. Emphysema

- Involves damage to the alveoli (air sacs) in the lungs, leading to reduced elasticity and impaired oxygen exchange.

- Results in shortness of breath, reduced lung capacity, and difficulty exhaling air fully.
- Often associated with a “barrel chest” appearance due to overinflated lungs. ^[2]

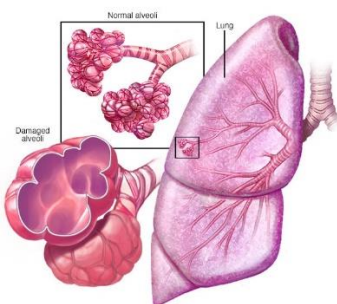


Figure No.2: Emphysema

Stages of COPD:

The severity of COPD is classified into four stages based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, which use forced expiratory volume in 1 second (FEV₁) from spirometry testing. The GOLD staging helps guide treatment decisions and predict disease progression.

Stage 1: Mild COPD (GOLD 1)

- FEV₁: $\geq 80\%$ of predicted value.

Stage 2: Moderate COPD (GOLD 2)

- FEV₁: 50%–79% of predicted value.

Stage 3: Severe COPD (GOLD 3)

- FEV₁: 30%–49% of predicted value.

Stage 4: Very Severe COPD (GOLD 4)

- FEV₁: $< 30\%$ of predicted value or $< 50\%$ with chronic respiratory failure. ^[1,2]

Causes:

The primary cause of COPD is exposure to irritants that damage the lungs and airways. Key factors include:

- **Smoking:** The leading cause of COPD, responsible for about 80%–90% of cases in developed countries.
- **Environmental Factors:** Long-term exposure to air pollution, industrial fumes, and second-hand smoke.
- **Occupational Hazards:** Inhalation of dust, chemicals, or fumes in workplaces.
- **Genetic Factors:** A deficiency of alpha-1 antitrypsin (AAT), a protein that protects the lungs, can predispose individuals to COPD.
- **Respiratory Infections:** Severe childhood infections may contribute to lung damage and increase COPD risk later in life. ^[1]

Symptoms:

COPD symptoms often develop slowly and worsen over time. Common symptoms include:

- **Chronic cough:** Often with mucus (phlegm) production.
- **Shortness of breath:** Especially during physical activity.
- **Wheezing:** A whistling or squeaky sound when breathing.
- **Fatigue:** Persistent tiredness due to reduced oxygen supply.
- **Frequent respiratory infections:** Including bronchitis and pneumonia.

As the disease advances, symptoms may include unintentional weight loss, swelling in the legs, and cyanosis (bluish discoloration of lips or fingers). ^[1]

Epidemiology:

COPD is a global health challenge:

- **Prevalence:** Over 300 million people worldwide are affected by COPD.
- **Mortality:** It is the third leading cause of death globally, accounting for approximately 3.2 million deaths annually.

- **Risk Factors:** Smoking is the predominant risk factor, but non-smoking-related cases are increasing in developing countries due to indoor pollution from cooking fuels.
- **Gender:** Historically more prevalent in men, but rates in women are rising due to smoking trends and environmental exposures. ^[2]

Etiology:

COPD results from a combination of genetic, environmental and behavioural factors:

- **Chronic Inflammation:** Long-term exposure to irritants causes inflammation, leading to narrowing of the airways and destruction of lung tissue.
- **Oxidative Stress:** Cigarette smoke and other pollutants increase oxidative damage, further worsening inflammation.
- **Imbalance of Protease-Antiprotease:** In individuals with AAT deficiency, protease enzymes destroy lung tissue, causing emphysema. ^[2]

Treatment:

Although COPD cannot be cured, treatments aim to manage symptoms, slow disease progression, and improve quality of life.

Medications:

1. **Bronchodilators:** Relax airway muscles, improving airflow (e.g., beta-agonists, anticholinergics).
2. **Inhaled Corticosteroids:** Reduce inflammation in moderate to severe cases.
3. **Combination Therapy:** Use of bronchodilators and corticosteroids for better symptom control.
4. **Phosphodiesterase-4 (PDE4) Inhibitors:** Reduce inflammation (e.g., roflumilast).
5. **Antibiotics and Antivirals:** Treat or prevent exacerbations caused by infections.

Non-Medication Therapies:

1. **Oxygen Therapy:** For individuals with advanced COPD and low oxygen levels.



2. Pulmonary Rehabilitation: A comprehensive program combining exercise, education, and support.
3. Surgical Interventions: Lung volume reduction surgery or lung transplants for severe cases. ^[1,3]

Prevention:

Preventing COPD involves addressing modifiable risk factors:

- Avoid Smoking: The most effective prevention strategy.
- Limit Exposure to Pollutants: Use masks in polluted areas and ensure proper ventilation in homes.
- Protective Equipment: For workers exposed to dust, fumes, or chemicals.
- Childhood Vaccinations: Prevent severe respiratory infections that could predispose to lung damage.
- Early Screening and Intervention: For high-risk individuals, especially smokers or those with a family history. ^[1,3]

PDE4 Inhibitors in COPD: Mechanism, Role, and Therapeutic Potential

Phosphodiesterase 4 (PDE4) inhibitors represent a significant advancement in the management of chronic obstructive pulmonary disease (COPD), particularly for patients with severe disease and frequent exacerbations. By targeting the inflammatory pathways central to COPD pathogenesis, PDE4 inhibitors help reduce symptoms, prevent flare-ups, and improve overall lung function. ^[4]

Role of PDE4 in COPD Pathophysiology

Phosphodiesterases (PDEs) are a family of enzymes that degrade cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), key secondary messengers involved in cellular signaling. Among the PDE family, PDE4 is the dominant isoform in inflammatory and immune cells such

as neutrophils, macrophages, T-cells, and airway epithelial cells.

In COPD, overactivation of PDE4 leads to:

- Decreased cAMP levels, impairing anti-inflammatory signaling.
- Increased inflammation by promoting the release of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF- α), interleukins (IL-6, IL-8), and leukotrienes.
- Exacerbations triggered by heightened immune responses.

By inhibiting PDE4, cAMP levels are restored, reducing inflammation and airway damage while improving respiratory outcomes. ^[5]

PDE4 Inhibitors: Mechanism of Action

PDE4 inhibitors act by blocking the breakdown of cAMP, leading to:

- Enhanced anti-inflammatory effects through reduced cytokine and chemokine production.
- Inhibition of neutrophil and eosinophil recruitment to the airways.
- Decreased airway remodeling and mucus hypersecretion.

These mechanisms collectively reduce chronic inflammation, which is a hallmark of COPD progression. ^[6]

Thiophene Scaffold in COPD: A Promising Avenue for Drug Development

The thiophene scaffold, a five-membered sulfur-containing heterocycle, has emerged as a versatile framework in drug design due to its unique chemical and pharmacological properties. In the context of chronic obstructive pulmonary disease (COPD), thiophene-based compounds are being explored for their potential to modulate key inflammatory and pathological processes, particularly as PDE4 inhibitors and anti-inflammatory agents. ^[7]

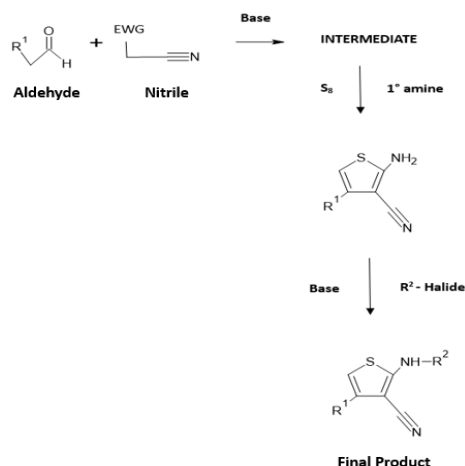
Anti-Inflammatory Potential of Thiophene Derivatives

COPD is characterized by chronic airway inflammation involving neutrophils, macrophages,



and pro-inflammatory cytokines. Thiophene-based compounds exhibit anti-inflammatory properties by targeting pathways such as:

1. NF- κ B Inhibition: Reducing the production of cytokines like TNF- α and IL-6.
2. Reactive Oxygen Species (ROS) Modulation: Counteracting oxidative stress in COPD.



Selection Of Biological Target:

A Protein Data Bank is a crystallographic database for three-dimensional structural data of large biological molecules such as Protein, Nucleic acid and Complex assemblies. In this study, Phosphodiesterase 4 (PDE4) inhibitors was chosen as a target for the treatment of COPD. The efficient PDB enzyme target was selected with lower resolution (PDB ID: 6LRM) provides a significant target for COPD therapeutic drugs. [10]

Construction of virtual library of ligands and novelty checking:

The ligands were drawn using the Chem Sketch software based on the necessary pharmacophoric features. Zinc15 and the Pubchem database were used to verify the novelty of the compounds. The designed compounds were considered to be novel since there is no data available in the ZINC® database. [10]

In-silico screening of drug likeness property:

Swiss ADME is a free web tool that predicts the Absorption, Distribution, Metabolism, and Excretion (ADME) properties of small molecules, along with other pharmacokinetic and

3. Matrix Metalloproteinase (MMP) Inhibition: Preventing extracellular matrix degradation and airway remodeling. [8,9]

MATERIALS AND METHODS:

Synthetic Scheme:

physicochemical characteristics. It is widely used in drug discovery and development to evaluate a compound's drug-likeness and optimize its pharmacological properties. [10]

In-silico screening of toxicity prediction:

The Osiris Property Explorer is a computational tool designed to predict the drug-relevant properties of chemical compounds. It provides a quick and intuitive way to estimate various molecular properties, including toxicity risks, physicochemical properties, and drug-likeness. It is widely used in the early stages of drug discovery and development for compound optimization. [10]

Molecular Docking:

Molecular docking is a computational method used to predict the interaction between a small molecule (ligand) and a target macromolecule (typically a protein or nucleic acid). It is a fundamental tool in structure-based drug design, used to identify potential drug candidates by modeling their binding pose and affinity. [10]

Post-Docking Analysis:

Molegro Molecular Viewer (MMV) is a user-friendly software tool for visualizing molecular

structures and analyzing interactions between proteins and ligands. It is particularly effective for post-docking analysis and offers various visualization options to explore binding poses, interaction networks (Hydrogen Bonds, Hydrophobic Interactions, Electrostatic Interactions) and molecular features.^[10]

RESULTS AND DISCUSSION:

Novelty assessment:

The designed 50 compounds were considered to be novel since there is no data available in the ZINC® and the Pubchem database.

In-silico screening of drug-likeness property:

As per Lipinski rule of 5, ADME properties of novel proposed analogues were assessed using Swiss ADME, a free web tool.

Table No.1: Drug-likeness property of novel proposed analogues

Compound code	Log P	Molecular weight	No. of HBA	No. of HBD	No. of Rot. bonds	Lipinski rule of 5 (n violation)
SS1	2.44	214.29	1	2	2	0
SS2	2.67	228.31	1	1	2	0
SS3	2.72	244.31	2	1	3	0
SS4	2.23	230.29	2	2	2	0
SS5	2.87	274.34	3	1	4	0
SS6	2.57	260.31	3	2	3	0
SS7	1.83	259.28	3	1	3	0
SS8	2.76	240.32	1	1	3	0
SS9	2.25	204.25	2	1	2	0
SS10	2.67	282.28	4	1	3	0
SS11	2.58	264.73	2	2	2	0
SS12	2.69	248.73	1	1	2	0
SS13	1.82	249.25	4	1	3	0
SS14	2.35	220.31	1	1	2	0
SS15	2.05	215.27	2	1	2	0
SS16	2.15	166.24	1	1	2	0
SS17	2.38	180.27	1	1	3	0
SS18	2.35	178.25	1	1	2	0
SS19	2.64	194.30	1	1	4	0
SS20	2.08	164.23	1	1	2	0
SS21	2.77	228.31	1	1	3	0
SS22	3.03	242.34	1	1	3	0
SS23	3.03	258.34	2	1	4	0
SS24	2.52	244.31	2	2	3	0
SS25	3.19	288.36	3	1	5	0
SS26	2.91	274.34	3	2	4	0
SS27	2.36	273.31	3	1	4	0
SS28	3.11	254.35	1	1	4	0
SS29	2.53	218.27	2	1	3	0
SS30	3.00	296.31	4	1	4	0
SS31	2.67	278.76	2	2	3	0
SS32	3.02	262.76	1	1	3	0
SS33	1.99	263.27	4	1	4	0
SS34	2.69	234.34	1	1	3	0
SS35	2.33	229.30	2	1	3	0
SS36	2.48	180.27	1	1	3	0
SS37	2.65	194.30	1	1	4	0

SS38	2.67	192.28	1	1	3	0
SS39	2.94	208.32	1	1	5	0
SS40	2.40	178.25	1	1	3	0
SS41	3.16	290.38	1	1	4	0
SS42	3.50	304.41	1	1	4	0
SS43	3.46	320.41	2	1	5	0
SS44	3.02	306.38	2	2	4	0
SS45	3.66	350.43	3	1	6	0
SS46	3.32	336.41	3	2	5	0
SS47	2.28	335.38	3	1	5	0
SS48	3.44	316.42	1	1	5	0
SS49	2.89	280.34	2	1	4	0
SS50	3.39	358.38	4	1	5	0

***In-silico* screening of toxicity prediction:**

Toxicity profile of novel proposed analogues was assessed using the Osiris Property Explorer.

Table No.2: Toxicity profile of novel proposed analogues

Compound code	Toxicity Prediction			
	Mutagenic	Tumorigenic	Irritant	Reproductive effect
SS1	✓	✓	✓	✓
SS2	✓	✓	✓	✓
SS3	✓	✓	✓	✓
SS4	✓	✓	✓	✓
SS5	✓	✓	✓	✓
SS6	✓	✓	✓	✓
SS7	✓	✓	✓	✓
SS8	✓	✓	✓	✓
SS9	✓	✓	✓	✓
SS10	✓	✓	✓	✓
SS11	✓	✓	✓	✓
SS12	✓	✓	✓	✓
SS13	✓	✓	✓	✓
SS14	✓	✓	✓	✓
SS15	✓	✓	✓	✓
SS16	✓	✓	✓	✓
SS17	✓	✓	✓	✓
SS18	✓	✓	✓	✓
SS19	✓	✓	✓	✓
SS20	✓	✓	✓	✓
SS21	✓	✓	✓	✓
SS22	✓	✓	✓	✓
SS23	✓	✓	✓	✓
SS24	✓	✓	✓	✓
SS25	✓	✓	✓	✓
SS26	✓	✓	✓	✓
SS27	✓	✓	✓	✓
SS28	✓	✓	✓	✓
SS29	✓	✓	✓	✓

SS30	✓	✓	✓	✓
SS31	✓	✓	✓	✓
SS32	✓	✓	✓	✓
SS33	✓	✓	✓	✓
SS34	✓	✓	✓	✓
SS35	✓	✓	✓	✓
SS36	✓	✓	✓	✓
SS37	✓	✓	✓	✓
SS38	✓	✓	✓	✓
SS39	✓	✓	✓	✓
SS40	✓	✓	✓	✓
SS41	✓	✓	✓	✓
SS42	✓	✓	✓	✓
SS43	✓	✓	✓	✓
SS44	✓	✓	✓	✓
SS45	✓	✓	✓	✓
SS46	✓	✓	✓	✓
SS47	✓	✓	✓	✓
SS48	✓	✓	✓	✓
SS49	✓	✓	✓	✓
SS50	✓	✓	✓	✓

Docking studies:

The ligands with novelty (0 identity), good drug-likeness properties and no toxicity were selected

for molecular docking studies against PDE4D inhibitors (PDB ID: 6LRM)

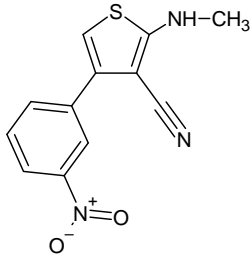
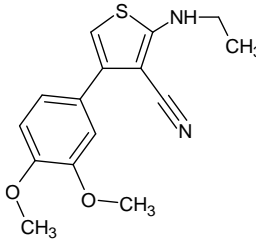
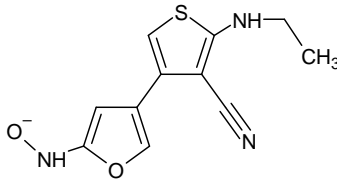
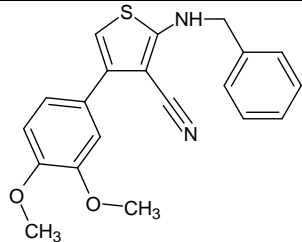
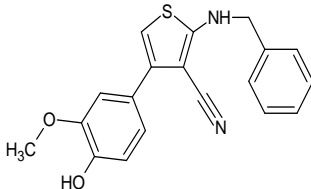
Table No.3: Binding score of novel proposed analogues

Compound code	PDE4D inhibitors (PDB ID: 6LRM)	Compound code	PDE4D inhibitors (PDB ID: 6LRM)
SS1	-6.37	SS26	-6.57
SS2	-6.97	SS27	-7.68
SS3	-6.76	SS28	-6.74
SS4	-6.82	SS29	-7.03
SS5	-7.08	SS30	-7.05
SS6	-6.88	SS31	-7.03
SS7	-7.92	SS32	-6.93
SS8	-6.69	SS33	-7.73
SS9	-7.18	SS34	-6.65
SS10	-6.77	SS35	-6.77
SS11	-6.82	SS36	-5.88
SS12	-6.92	SS37	-5.64
SS13	-7.69	SS38	-6.01
SS14	-6.65	SS39	-5.66
SS15	-6.77	SS40	-5.71
SS16	-6.0	SS41	-7.28
SS17	-6.18	SS42	-6.86
SS18	-6.38	SS43	-7.43
SS19	-6.19	SS44	-7.04
SS20	-6.06	SS45	-8.67



SS21	-6.65	SS46	-7.83
SS22	-6.86	SS47	-7.1
SS23	-6.77	SS48	-6.99
SS24	-6.62	SS49	-7.57
SS25	-7.71	SS50	-7.5

Table No.4: Structure / IUPAC name of top 5 ligands based on docking scores

Compound code	Ligand structure	IUPAC name
SS7		2-(methylamino)-4-(3-nitrophenyl)thiophene-3-carbonitrile
SS25		4-(3,4-dimethoxyphenyl)-2-(ethylamino)thiophene-3-carbonitrile
SS33		2-(ethylamino)-4-(5-nitrofuran-3-yl)thiophene-3-carbonitrile
SS45		2-(benzylamino)-4-(3,4-dimethoxyphenyl)thiophene-3-carbonitrile
SS46		2-(benzylamino)-4-(4-hydroxy-3-methoxyphenyl)thiophene-3-carbonitrile

Post-Docking Analysis:

To visualize molecular structures and analyze interactions between protein and ligands, Molegro Molecular Viewer (MMV) software is used.

Table No.5: Docking interaction of top 5 ligands based on docking scores

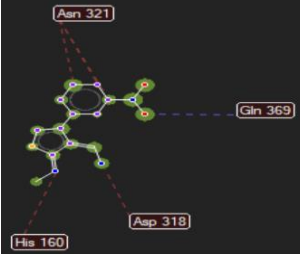
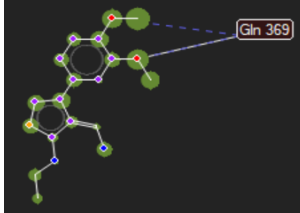
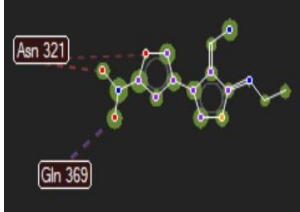
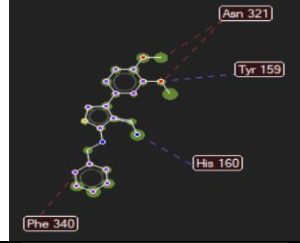
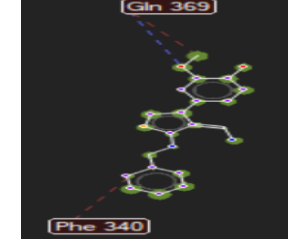
Compound code	Docking interaction
SS7	
SS25	
SS33	
SS45	
SS46	

Table No.6: Ligand-Receptor interaction

Compound code	Hydrogen bond interaction
SS7	Gln 369
SS25	Gln 369
SS33	Gln 369
SS45	Tyr 159, His 160
SS46	Gln 369

CONCLUSION:

This study demonstrates the utility of *in-silico* drug design and molecular docking techniques in identifying novel thiophene derivatives as potential PDE4D inhibitors for COPD treatment. The computational findings suggest that these compounds exhibit strong binding affinities and favorable pharmacokinetic profiles, making them promising candidates for further experimental validation. The insights gained from the docking

analysis and SAR exploration pave the way for the development of effective and selective PDE4D-targeted therapies, potentially improving outcomes for COPD patients.

ACKNOWLEDGEMENT

We express our sincere thanks to the Department of Pharmaceutical Chemistry, College of Pharmacy, Madras Medical College (MMC), Chennai for providing necessary facilities for the research work.

Conflicts Of Interest

The author declares there is no conflict of interest.

REFERENCES

1. Rodrigues SO, Cunha CMCD, Soares GMV, Silva PL, Silva AR, Gonçalves-de-Albuquerque CF. Mechanisms, pathophysiology, and currently proposed treatments of chronic obstructive pulmonary disease. Basel: Pharmaceuticals; 2021.
2. Hikichi M, Mizumura K, Maruoka S, Gon Y. Pathogenesis of chronic obstructive pulmonary disease (COPD) induced by cigarette smoke. 1st ed. Thoracic Disease: Journal of Thoracic Disease; 2019.
3. MacLeod M, Papi A, Contoli M, Beghé B, Celli BR, Wedzicha JA, et al. Chronic obstructive pulmonary disease exacerbation fundamentals: Diagnosis, treatment, prevention and disease impact. Vol 26. Sydney: Respirology; 2021.
4. Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. 1st ed. Oxford: Cochrane Database of Systematic Reviews; 2017.
5. Michalski JM, Golden G, Ikari J, Rennard SI. PDE4: A novel target in the treatment of chronic obstructive pulmonary disease. 1st ed. Massachusetts: Clinical Pharmacology & Therapeutics; 2011.
6. Boswell-Smith V, Spina D. PDE4 inhibitors as potential therapeutic agents in the treatment of COPD—focus on roflumilast. London: International Journal of Chronic Obstructive Pulmonary Disease; 2007.
7. Mishra R, Kumar N, Sachan N. Synthesis, pharmacological evaluation, and in-silico studies of thiophene derivatives. 1st ed. China: Oncologie; 2021.
8. Chaudhary A, Jha KK, Kumar S. Biological diversity of thiophene: A review. New Delhi: Journal of Advanced Scientific Research; 2012.
9. Revelant G, Dunand S, Hesse S, Kirsch G. Microwave-assisted synthesis of 5-substituted 2-aminothiophenes starting from arylacetaldehydes. Stuttgart: Synthesis; 2011.
10. Singh N, Chaput L, Villoutreix BO. Virtual screening web servers: designing chemical probes and drug candidates in the cyberspace era. 2nd ed. London: British Journal of Pharmacology; 2021.

HOW TO CITE: Neelambari S.*, Priyadharshini R., Mohammed Idrees H., Jawaharsamuel R., In-Silico Drug Design and Molecular Docking Studies of Some Novel Thiophene Derivatives Targeting Pde4d Inhibitors as Chronic Obstructive Pulmonary Disease Agents, *Int. J. of Pharm. Sci.*, 2025, Vol 3, Issue 1, 444-454. <https://doi.org/10.5281/zenodo.14609519>

