PYRIMIDINE ANALOGUES AS ANTI-NEURODEGENERATIVE AGENTS

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DECLARATION

We, **ANJALI & YASH KHANEJA**, hereby declare that the work which is being submitted in this dissertation entitled "PYRIMIDINE ANALOGUE AS ANTI-NEURODEGENERATIVE AGENTS" in the partial fulfilment for the award of the degree of **Master of Science** in the **Department of Applied Chemistry**, Delhi Technological University is an authentic record of our own work carried out during the period from **August, 2025 to May, 2026** under the supervision of **Dr. Richa Srivastava (Associate Professor, Department of Applied Chemistry, Delhi Technological University)**.

We further declare that the dissertation has not been submitted by us for the award of any other degree of this or any other Institute.

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CERTIFICATE

This is to certify that the Project report entitled "PYRIMIDINE ANALOGUE AS ANTI-NEURODEGENERATIVE AGENTS" which is submitted by **ANJALI (24/MSCCHE/64)** and YASH KHANEJA **(24/MSCCHE/46)**, Department of Applied Chemistry, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of **Master of Science**, is a record of the project work carried out by the students under my supervision. To the best of my knowledge, this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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ABSTRACT

Neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic Lateral Sclerosis (ALS), and Multiple Sclerosis (MS) altogether comprise one neurodegenerative mechanisms involved in the disease development. This dissertation attempts to investigate the possibility of using the pyrimidine derivatives as neuroprotective agents, particularly emphasizing on their polypharmacology profiles. Pyrimidine, a heteroaromatic compound with six members containing a nitrogen atom, is well-known for its chemical diversity, brain penetration, favorable physiochemical properties, and ability to interact with different biological receptors related to neurodegeneration. Among the important pathologic processes that have been considered in this research project are aggregation of amyloid-β, tau protein hyperphosphorylation, neurotransmitter imbalance (cholinergic and dopaminergic systems), oxidative stress associated with monoamine oxidase-B (MAO-B) and chronic neuroinflammation. A systematic SAR study was conducted with a view to finding out how structural variations in certain positions in the pyrimidine scaffold affected the enzymes' binding affinity, lipophilicity, selectivity towards various types of receptors and central nervous system penetration. Functional groups examined within the context of this work included amino groups, diamino groups, styryl groups and electron donating/withdrawing substituents as regards their effects on the inhibitory activity of acetylcholinesterase (AChE), butyrylcholinesterase (BuChE) and monoamine oxidase B (MAO-B). Experimental work entailed in silico molecular docking of some selected pyrimidines against three neurodegeneration-related protein targets: monoamine oxidase B (PDB: 2BYB), acetyl-cholinesterase (PDB: 4BDT) and butyrylcholinesterase (PDB: 6QAB). In silico docking was done using recognized computational software, while docking scores were determined based on molecular interaction between the proteins and ligands. Among the selected pyrimidines, compound numbers 19 and 22 exhibited remarkable binding to MAO-B, while compounds 10 and 22 had favourable docking scores against acetylcholinesterase and butyryl-cholinesterase respectively. This study has established an excellent computational platform that will guide the future development of drugs based on pyrimidine compounds to target the highly complicated neurodegenerative pathways.

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CHAPTER 1
INTRODUCTION

1.1Introduction to Neurodegenerative Disorders

Neurodegenerative disorders (NDs) are a group of chronic, debilitating and progressive diseases pictured by the gradual degeneration and death of neurons in the central and peripheral nervous systems. These disorders affect the brain, peripheral nerves, and spinal cord, resulting in confusion, memory loss, trouble thinking or concentrating, slowed movements, shaking and tremors, balance problems and behaviour changes. Neurodegenerative diseases are usually irreversible because neurons retain limited regenerative capacity.[1-3]. Neurodegenerative diseases represent one of the greatest medical challenges worldwide due to increasing life expectancy and aging populations. According to previous investigations, NDs are reported to have a limited survival rate. Most recently, in 2019, a total of 10 million deaths and 349.2 million individuals were affected by major neurological disorders worldwide.[4] According to the World Health Organization (WHO), neurological disorders are currently one of the leading causes of disability and death worldwide.[5] Recent global reports estimated that more than 55 million people are living with dementia, and approximately 10 million new dementia cases are diagnosed every year.[6] According to recent studies, more than 10 million people worldwide are affected by Parkinson's disease, and its prevalence has doubled during the past 25 years.[7] Similarly, Amyotrophic Lateral Sclerosis (ALS) affects nearly 2–5 individuals per 100,000 population, while Huntington's disease affects approximately 5–10 individuals per 100,000 population in Western countries.[8,9] Multiple sclerosis currently affects nearly 2.8 million people worldwide.[10] This vast group of neurodegenerative diseases mainly includes alzheimer's disease (AD), parkinson's disease (PD), huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and diabetic neuropathy (DN).[1-3] The pathophysiology of neurodegenerative disorders is progressive neuronal dysfunction associated with abnormal protein aggregation, oxidative stress, mitochondrial dysfunction, excitotoxicity, chronic neuroinflammation, impaired autophagy, and synaptic degeneration. Each disease is characterized by specific protein abnormalities.[1,3] Currently some marketed drugs used for the treatment of these disease are donepezil, rivastigmine, galantamine, memantine for AD, levodopa, piribedil, pramipexole, apomorphine, for PD.[1] Their single target nature and inability to modify disease progression make them inadequate and demands the exploration of newer therapies envisioning newer chemical moieties to treat these diseases.[1] Pyrimidine emerged as a crucial heterocyclic moiety that has gained broad interest for its therapeutic potential against NDs also due to its ability of blood brain barrier penetration.[11,12]

1.2 Diseases associated with neurodegeneration:

1.2.1Multiple sclerosis:

Multiple Sclerosis is a chronic inflammatory and autoimmune disease of the central nervous system that mainly affects the brain and spinal cord.[13] It is immune-mediated because the immune system mistakenly attacks the myelin sheath, a protective covering surrounding neuronal fibers. Damage to myelin results in demyelination, inflammation, and progressive neuronal injury, this condition ultimately disturbing the normal propagation of electrical impulses along nerve pathways.[13,14] As a result, patients experience various neurological abnormalities, manifestations of which encompass fatigue, impaired coordination, muscular weakness, reduced mobility, numbness of tingling sensations, visual disturbances such as blurred or double vision, and cognitive dysfunction.[13].

1.2.2 Amyotrophic lateral sclerosis (ALS):

Amyotrophic Lateral Sclerosis, also referred as Lou Gehrig's disease, is a s progressive degenerative neurological disorder that primarily leads to deterioration of motor neurons present in the brain and spinal cord.[15] Motor neurons are accountable for controlling voluntary muscular movements, and their gradual deterioration diminishes communication between the nervous system and skeletal muscles. With progresses of disease, the brain gradually loses it's ability to regulate muscle activity, resulting in severe physical disability.[15,16] ALS is mainly categorised into two forms: sporadic ALS, which occurs without a clear family history, and familial ALS, which is genetically inheritable.[17] Common symptoms experienced by patients of ALS are progressive muscle weakness, difficulty in speaking, swallowing problems, muscle atrophy, impaired coordination, and respiratory complexity.

1.2.3 Huntington's disease (HD)

Huntington's Disease is a rare, progressive inherited neurodegenerative disorder affecting both physical and cognitive functions. The disease occurred due to mutation in the huntingtin (HTT) gene, which leads to formation of an abnormal huntingtin protein, that damages specific regions of the brain, leading to motor, behavioural dysfunction, cognitive decline, and psychotropic deficits. Huntington's disease is inherited through autosomal dominant manner, indicating that inheritance of a single copy of defective gene from either parent is sufficient for development of disorder.[18-20] Some common clinical manifestations include involuntary movements, behavioural disturbances, impaired coordination, depression, memory impairment, and progressive decline in cognitive abilities.

1.2.4 Parkinson's disease (PD):

Parkinson's Disease is a progressive neurodegenerative disorder mainly characterized by decline in motor functions.[21] This disease often results due to deterioration of neuron that produces dopamine in the region called substantia nigra in the brain. Dopamine is an important neurotransmitter, necessary for regulation and coordination of voluntary muscular movements. Diminishing in dopamine levels disrupts normal neuronal signaling and leads to motor dysfunction.[22,23] The actual cause of Parkinson's disease is not well understood; however,

both genetic and environmental factors are thought to contribute to disease development.[24] Common mltor symptoms include tremors, impaired balance bradykinesia, postural instability, muscular rigidity, and slowed body movements, patients may also experience several non-motor symptoms such as sleep disturbances, depression, mood disorders, cognitive decline, and autonomic dysfunction.[25] Currently no single diagnostic test is available, diagnosis mainly depends on clinical evaluation, neurological examination, and assessment of patient history.[26] Although complete cure has not been established yet, current treatment facilities majorly focusing on symptomatic relief and patient quality of life. Currently some marketed drugs such as levodopa, piribedil, pramipexole, apomorphine, selegiline, rasagiline, safinamide, entacapone are in use for the treatment of PD.[27] Levodopa is the most commonly used drug and acts as a dopamine replacement, is often used for controlling motor symptoms. Furthermore, additional therapeutic agents such as dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors are also used for disease modification.[27,28] Ongoing research is mainly focused on understanding the molecular mechanisms involved in deterioration of neuron that produces dopamine and developing more effective therapeutic drugs for disease management.[28]

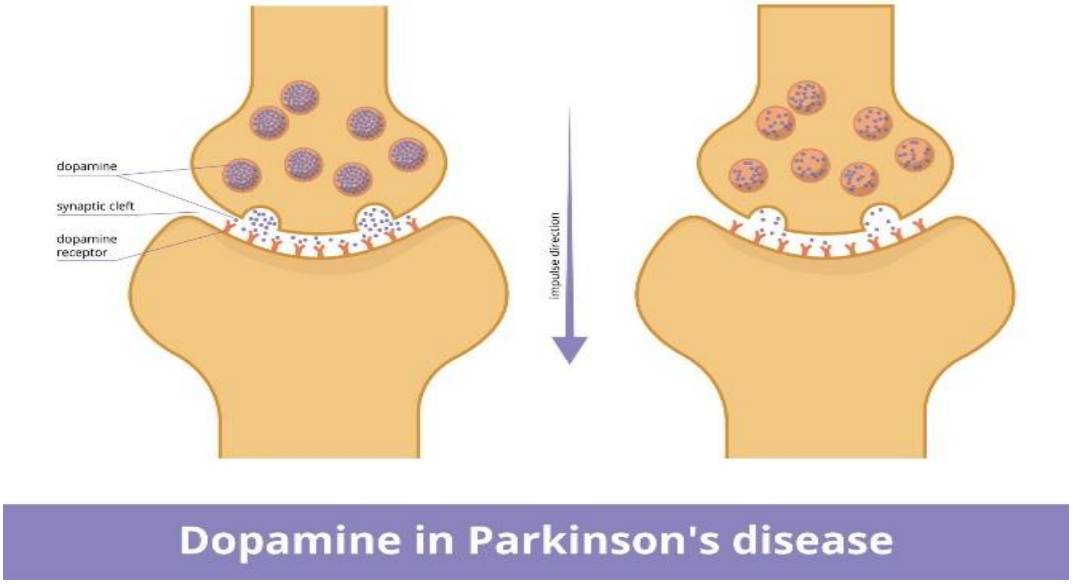


Fig1.1: Degeneration of Dopaminergic Neurons in Parkinson's Disease

1.2.5 Alzheimer's disease (AD):

Alzheimer's disease(AD) is a neurodegenerative disorder which represents one of the most prevalent cause of dementia worldwide. This disease is named after Dr. Alois Alzheimer. Clinically, it is characterised by a gradual decline in memory, cognitive deterioration, and behavioural alteration due to neuronal loss.[29-31] The significant pathophysiology of Alzheimer's disease include abnormal protein aggregation[32](amyloid plaques, intracellular neurofibrillary tangles)[33,34], neurotransmitter imbalance, oxidative stress(MAO),[35] neuroinflammation[36], and excitotoxic neuronal damage. These pathophysiological events are interconnected and collectively result in synaptic dysfunction and neuronal loss[37]. So,

targeting single pathway is an inefficient strategy for the complete treatment of disease, Research should be focused on multitargeted ligands[38]. Currently FDA(Food and Drug Administration) approved drugs such as tacrine, donepezil, rivastigmine, galantamine, memantine, aducanumab provide symptomatic relief only with little efficacy to prevent the progression of the disease.[39-44] Diversity in pathophysiology of disease, necessitate a crucial need to discover effective drugs to understand disease causes better. In this regard, the potentials of pyrimidine have been widely studied as anti-Alzheimer's agents.

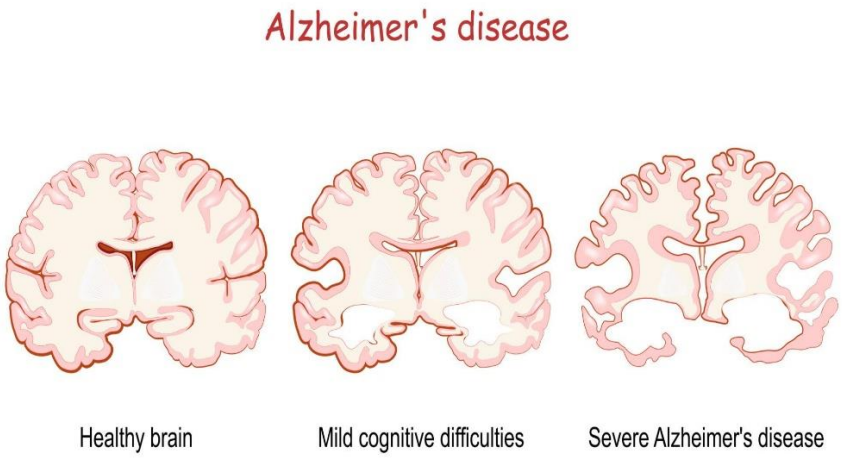


Fig1.2: Brain Changes Associated with Alzheimer’s Disease

1.3 Pathophysiology of Neurodegenerative Disorders

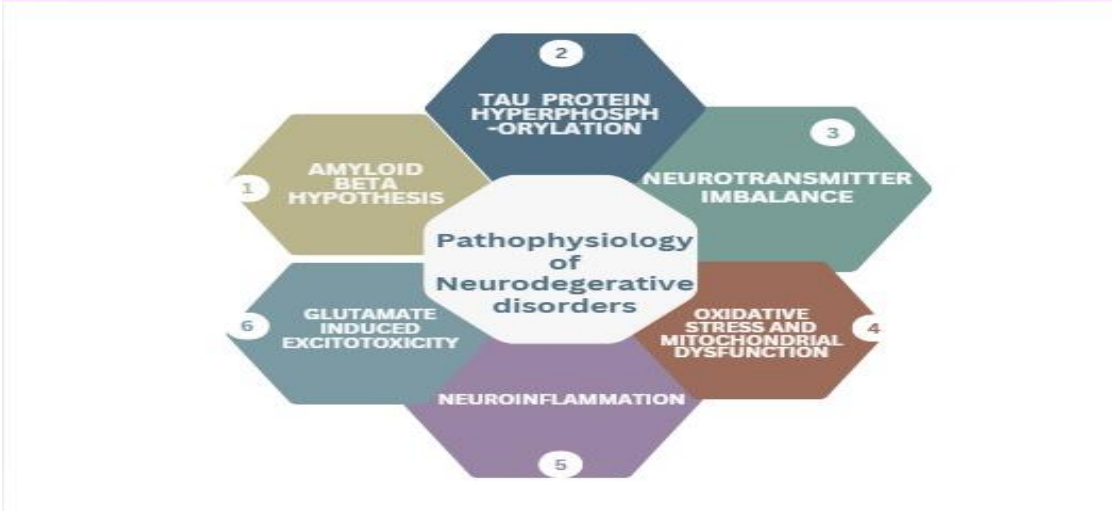


Fig 1.3: Pathophysiology of Neurodegenerative Disorders

1.3.1 Amyloid Beta hypothesis (Protein Misfolding and Aggregation)

The amyloid Beta hypothesis proposes that abnormal cleavage of amyloid precursor protein (APP) by β- and γ-secretases produces amyloid-β (Aβ) peptides, particularly Aβ_{1-42}. These peptides are sticky and aggregate due to attraction with other protein to form soluble oligomers and insoluble extracellular plaques outside neurons that disrupt cell signaling, induce oxidative

stress, and trigger inflam**mat**ory responses. AChE also plays a critical role in accelerating amyloid beta aggregation.[45-47]

1.3.2 Tau Protein Hyperphosphorylation (Protein Misfolding and Aggregation)

Tau is a microtubule-associated protein responsible for maintaining cells internal transport system. In Alzheimer's disease, tau become abnormal hyperphosphorylated, detaches resulting in the formation of intracellular neurofibrillary tangles inside neuron. These tangles disrupt nutrient transport and leading to cell death which strongly correlate with cognitive decline.[48,49] In PD and HD, there are also misfolded Tau proteins.

1.3.3 Neurotransmitter Imbalance

Neurotransmitter Imbalance is also associated with neurodegenerative diseases. Change in levels of neurotransmitters impair communication between neurons might impact normal brain functions. Deduction in dopamine levels is observed in Parkinson's disease, whereas decreased in acetylcholine levels is commonly associated with Alzheimer's disease. Therefore, neurotransmitter disturbances lead to memory impairment, cognitive decline, behavioural abnormalities, and motor dysfunction.[50,51]

1.3.4 Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is recognised as another major cause of neurodegenerative disease. It alter the biochemical and biomolecular parts of body, leading to diseases such as MS, AD, PD, HD,ALS,. Reactive Oxygen Species(ROS) and Reactive Nitrogen Species(RNS) in the brain act as critical signaling molecule but excess of these reactive species can cause neurodegeneration or dying of nerve cells. Oxidative stress can also induced due to impaired mitochondrial function, because mitochondria mainly make intracellular ROS. Break down of oxygen molecule can produce superoxide anion which can further produce hydrogen peroxide, hydroxyl radical, hydroperoxyl radical, hypochlorous acid. MAO-B is a flavoenzyme located in the outer mitochondrial membrane which catalyse the oxidative deamination of neurotransmitters resulting in production of hydrogen peroxide. Therefore, MAO-B is another major cause of oxidative stress. Catalase enzyme helps to maintain the amount of hydrogen peroxide. NADPH oxidase is an enzyme that makes ROS. ROS and RNS can damage lipids, proteins, DNA and RNA which accelerates neurodegeneration.[52-56]

1.3.5 Neuroinflammation

Neuroinflammation is a process where central nervous system gets inflamed. Normally, neuroinflammation helps protect the brain, but excess of it harm the brain. Microglia and astrocytes are primary cell in brain which cause inflammation, and chronic activation of them leads to sustained release of inflammatory cytokines, including Nuclear factor kappa B(NF-kB), TNF-α and IL-1β. Rather than being protective, prolonged neuroinflammation exacerbates neuronal injury. From the recent observation it was evident that inflammation in brain leads to many neurodegenerative disease such as AD,

PD, HD, MS, ALS. So, it's become crucial to find ways to target this inflammation to control neurodegeneration.[57,58]

1.3.6 Glutamate-Induced Excitotoxicity

Glutamate is the neurotransmitter in the brain, but due to excessive activation in postsynaptic neurons (such as NMDA receptors) cause neuronal damage, leads to neurodegeneration. It also causes abnormal calcium influx, leading to mitochondrial dysfunction and apoptotic neuronal death. Although, complete inhibition of NDMA receptor has resulted in severe side effects. Recently used memantine is an uncompetitive NDMA receptor antagonist. But for multi target ligand, pyrimidine derivatives can be a good choice.[59]

1.4 Pyrimidine Analogues as Anti-Neurodegenerative Agents

1.4.1 Historical Background of Pyrimidine

Pyrimidines is a six membered heterocyclic compound having nitrogen at position 1 and 3[60]. The history of pyrimidine dates back to the nineteenth century when nitrogen containing heterocyclic compounds were broadly investigated for their chemical and biological properties. Pyrimidine has gained significant scientific importance after the discovery that naturally occurring pyrimidine bases such as cytosine, thymine, and uracil are essential structural components of nucleic acids including DNA and RNA, which play a crucial role in genetic information storage, protein synthesis, cellular metabolism, and regulation of numerous physiological processes. The structural resemblance of pyrimidine analogues to endogenous nucleic acid bases encouraged researchers to synthesize various pyrimidine analogues for therapeutic applications.[61] During the twentieth century, pyrimidine derivatives emerged as important pharmacological agents exhibiting antiviral, anticancer, antimicrobial, anti-inflammatory, anti-hypertensive, anti-epileptic, anticonvulsant, anti-oxidant, analgesic, anti-diabetic, and anti-tubercular, and neuroprotective properties. With advances in medicinal chemistry and computational drug design, pyrimidine-based compounds became an important area of research for neurodegenerative disorders because of their ability to interact with multiple biological targets involved in neuronal degeneration, strong hydrogen bonding capability, and their favourable blood–brain barrier permeability and for their synthesising practicability and non-poisonous nature.[61-66]

1.4.2 Physical properties of pyrimidine

Pyrimidine is generally colourless or pale crystalline solid or liquid with a characteristic mild odour. This compounds usually exhibit moderate molecular weight and planar molecular geometry. Most pyrimidine derivatives possess good thermal stability with relatively high melting points due to their aromatic nature. These are highly soluble in polar solvents such as water, ethanol, methanol, while some substituted derivatives also show solubility in organic solvents because of the presence of nitrogen atoms that increase polarity. The dipole moment of pyrimidine is higher than benzene because of the electronegative nitrogen atoms in the ring, resulting in stronger intermolecular interactions. Many pyrimidine analogues possess moderate

lipophilicity and favourable crystallinity, which influence their physicochemical behaviour.[61,62]

1.4.3 Chemical properties of pyrimidine

Pyrimidines is a six membered heterocyclic compound having nitrogen at position 1 and 3. Pyrimidine is aromatic in nature due to the presence of six delocalized π-electrons within the ring system, which provides remarkable chemical stability. It is electron deficient in nature due to presence of two electronegative nitrogen atom.[60] Therefore, pyrimidine undergoes nucleophilic substitution reactions more readily than electrophilic substitution reactions[60,67]. Pyrimidine also exhibits weak basic character because the lone pair electrons on the nitrogen atoms participate partially in aromatic electron delocalization. The ring structure possesses great ability to participate in hydrogen bonding interactions, which significantly enhances its binding affinity with enzymes, receptors, and nucleic acids.[66,67] Due to structural versatility of pyrimidine different substitutions can be introduced at various positions of the pyrimidine ring to modify lipophilicity, electronic distribution, receptor affinity, and pharmacological activity[64]. Such modifications enable medicinal chemists to design pyrimidine derivatives with improved biological efficacy and enhanced blood–brain barrier penetration. These favourable physicochemical attributes make pyrimidine an priviliged scaffold for the development of drugs targeting central nervous system disorders.[63,67]

1.4.4 Pyrimidine Analogues as Anti-Neurodegenerative Agents

Neurodegenerative diseases involve complex pathological mechanisms including protein aggregation, oxidative stress, mitochondrial dysfunction, neuroinflammation, excitotoxicity and neurotransmitter imbalance. Pyrimidine analogues have emerged as promising therapeutic agents because of their multi-target therapeutic actions simultaneously.[63,64,67] Like, Certain pyrimidine compounds also demonstrate monoamine oxidase-B inhibitory activity, thereby increasing dopamine availability and reducing motor dysfunction associated with Parkinson's disease. Recent studies have also demonstrated that pyrimidine analogues can inhibit neuroinflammatory mediators such as tumour necrosis factor-α, interleukin-1β, and nuclear factor-kappa B, thereby reducing inflammation-induced neuronal injury. Some pyrimidine compounds are capable of preventing amyloid-β aggregation and tau hyperphosphorylation, which are major pathological features of Alzheimer's disease.[63-67] Furthermore, pyrimidine derivatives may protect neurons from apoptosis and mitochondrial dysfunction, thereby enhancing neuronal survival and neuroprotection. The favourable physicochemical properties of pyrimidine, including blood–brain barrier penetration, receptor binding affinity, structural flexibility, and multi-target therapeutic action, potential disease-modifying effects, lower toxicity and enhanced biocompatibility make pyrimidine analogues highly promising candidates for the development of novel anti-neurodegenerative agents.[63,64,66,67]

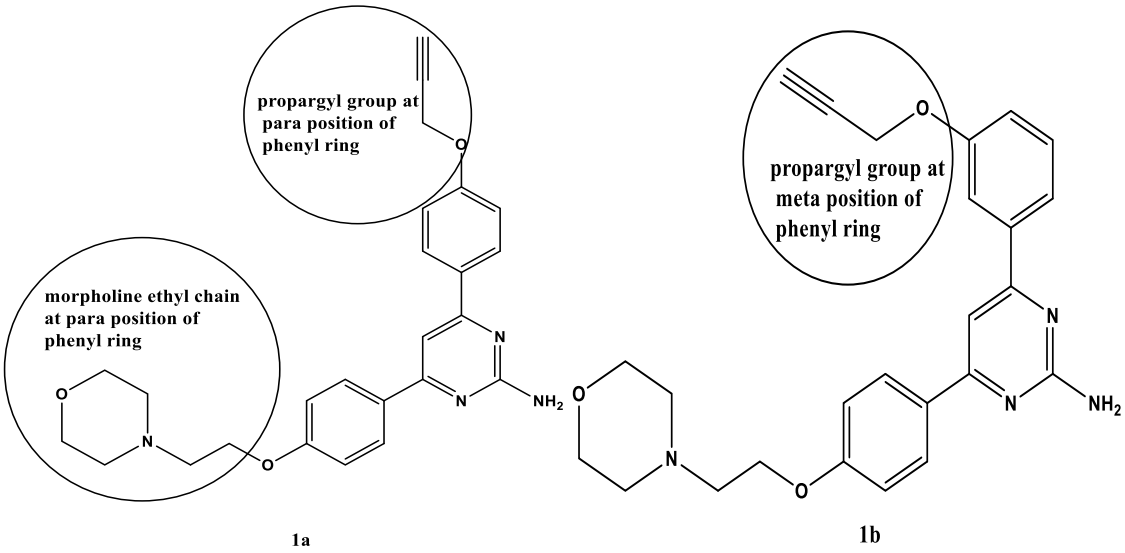
CHAPTER 2
LITERATURE REVIEW

2.1 Pyrimidine analogues against specific neurodegenerative disorders

Diversity in pathophysiology of disease, necessitate a crucial need to discover effective drugs to understand disease causes better. In this regard, ongoing research for development of better therapeutic agents against neurodegenerative disorders is mainly focusing on pyrimidine derivatives due to their better binding affinity with internal bases of protein's active sites and their multitarget ability makes it even more efficient. Main focus of this is more aligned towards alzheimer's and parkinson's disease.

Kumar et al. formulated, synthesised, analysed a series of 4,6-diphenylpyrimidine derivative for AD. Compound 1a exhibit most potent inhibition of Monoamine oxidase-A (MAO-A) with IC_{50} value of 18.34 ± 0.38 nM, BuChE enzymes with IC_{50} value of 0.666±0.03 nM and AChE inhibition with IC_{50} value of 30.46 ± 0.23 nM. Compound 1b exhibit most potent AChE inhibition with IC_{50} value of 9.54+70.42nM and MAO-A inhibition with IC_{50} value of 1010 ± 70.42nM. These compounds also shows neuroprotective properties against 6-OHDA and H_2O_2 induced neurotoxicity in SH-SY5Y cells. SAR analysis shows that propargyl group involved in covalent bond formation with FAD co-factor of MAO enzyme and piperidine/morpholine ring act as pharmacophore for AChE enzyme. The chain length between the morpholine and propargyl moieties is reported to control the dual interactions of these moieties with both the catalytic active site(CAS) and peripheral anionic site(PAS) of the AChE enzyme. These compound were found to be reversible inhibitors of MAO-A and AChE.[68]

Han et al. formulated, synthesised, analysed a series of 2-(2-oxoethyl) pyrimidine-5-carboxamide derivatives as acetyl cholinesterase inhibitors (AChEIs) for AD. Compound 2 exhibit most potent inhibition of acetylcholinesterase (AChE) with IC_{50} value of 0.88±0.78 μM, which was better than that of Huperzine-A(IC_{50}= 5.28 ±1.20 μM). SAR analysis shows that presence of thiophene ring in replacement of benzene ring shows significantly improved inhibition. The amide chain with three carbon at the C-5 of pyrimidine gave the compounds enough length and flexibility so the molecules can smoothly have dual binding with both the catalytic active site (CAS) and peripheral anionic site (PAS) of acetylcholinesterase(AChE). The com pounds with electron withdrawing groups (–NO_2) of benzene ring shows great impact on the activity.[69]



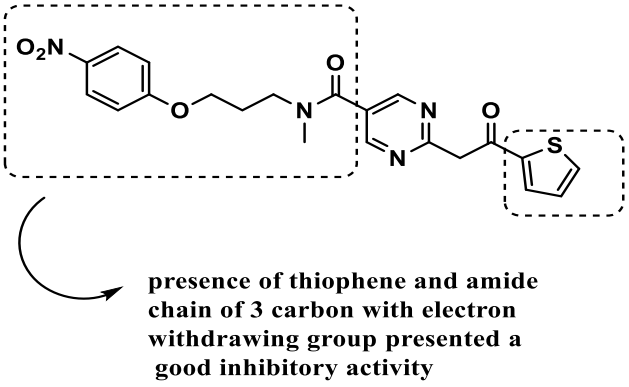


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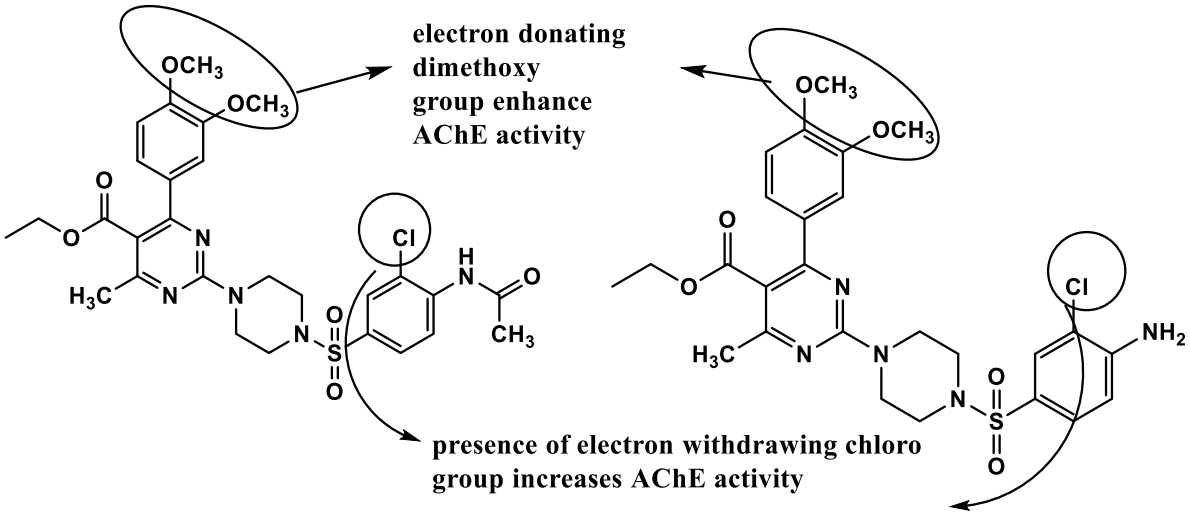
Fig2.1: Chemical structure of compounds (1-2) as anti-alzheimer's agent

Manzoor et al. formulated, synthesised, analysed a series of phenyl sulfonyl-pyrimidine carboxylate hybrids as multifunctional agents for AD. Compound 3 and 4 exhibit most potent inhibition of acetylcholinesterase (AChE); IC50=47.33 ± 0.02 nM and 51.36 ± 0.04 nM and moderate inhibition against butyrylcholinesterase (BuChE);IC_{50}=159.43 ± 0.72 nM and 153.3 ± 0.74 nM respectively. SAR analysis shows that presence of 3,4-disubstituted electron-donating groups (-OCH3) and electron-withdrawing group(-Cl) increases the binding affinity towards AChE. Further molecular docking possesses, the 3,4-dimethoxyphenyl group of compound 3 is engaged in p-p stacking interaction with Trp279 residues (distance 3.8 Å) at PAS and the aromatic ring of the 4-acetamido-3-chlorobenzenesulfonyl group of compound 3 is involved in sandwich-type p-p stacking with residue Trp84 (distance 4.1 Å) at CAS. Therefore, this observed result implicated that the compound 3 and 4 showed highest AChE inhibitory activity in comparison to standard drug donepezil. Both compounds showed impressive neuroprotection in MC65 cell line assay at 80 mM. Compound 3 and 4 with permeability (Pe) values of 24.3 $\times 10^{-6}$ and 23.7 $\times 10^{-6}$ cm/s respectively, indicates high potential for blood-brain barrier (BBB) permeability. This study suggest that these derivatives could act as most effective MTDLs and could be regarded as a promising “lead” for AD therapy.[70]

Jain et al. designed, synthesised, analysed a series of 2,4,6-substituted pyrimidine derivatives as BACE-1 (β-secretase) inhibitors for the treatment of AD. All the synthesised compound were orally bioavailable and exhibit high BBB permeability. BACE-1 in-vitro assay by Fluorescence Resonance Energy Transfer (FRET) technique revealed that compound 5 exhibit maximum inhibition of 73.91% at 10μM concentration and have IC50=6.92±0.02μM. SAR analysis revealed that presence of bulky benzyloxy group at meta position of ring A with o,p-dichloro on ring B significantly improved BACE-1 inhibition. Molecular docking revealed that amino group have key interactions with the aspartate dyad (Asp32: 3.29Å, 3.57Å; Asp228: 2.72Å, 2.82Å), showed hydrogen bonding with Gly230 (2.48Å) and π-π stacking was observed between Tyr71 and pyrimidine nucleus and nitrogen at the pyrimidine ring also had interaction with Val332. This observed outstanding interaction pattern make compound 5 as potent BACE-1 inhibitor.[71]

Fang et al. designed, synthesised and biologically evaluated twenty-eight compounds derived from resveratrol (stilbenes) and GIBH-130 (piperazinyl pyrimidines) for treatment of AD. These compounds were certified for their anti-neuroinflammatory activity in BV2 cells. From these compounds, Compound 6 shows better inhibition of nitric oxide, tumor necrosis factor-a, and interleukin-1b (NO, TNF-a, IL-1b are inflammatory mediators) production with IC50 values of 1.0, 2.6, and 0.5mM, respectively and. SAR analysis demonstrate that presence of -CF_3 on ring B enhance NO inhibition. Druggability of this compound improved by increasing the distance between two benzene ring A and B. Further observations from Parallel artificial membrane permeation assay (PAMPA) revealed that compound 6 have high blood-brain penetration whereas standard drug-Resveratrol shows medium penetration. Also bioavailability of resveratrol is low. Therefore, these derivatives could act as promising leads for further development as a new anti-AD therapeutic agents.[72]



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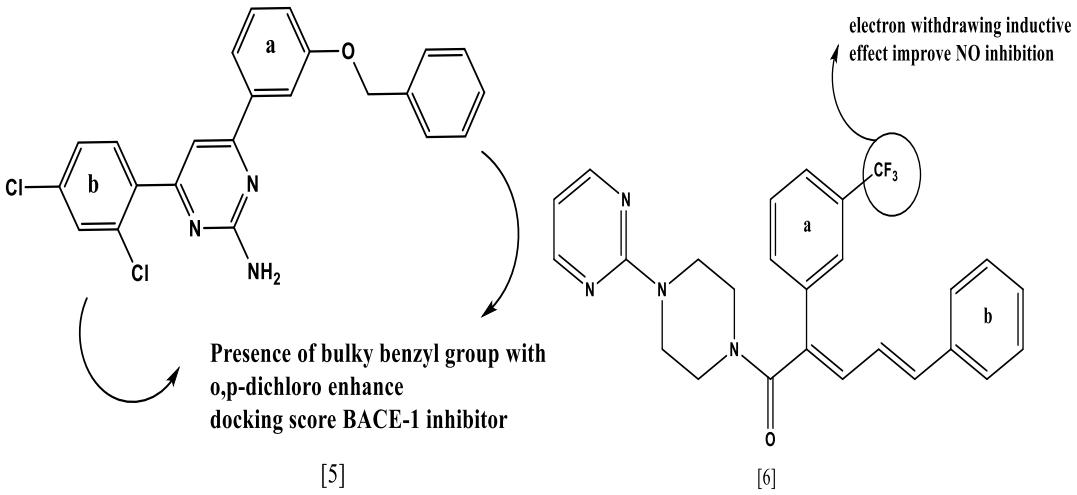
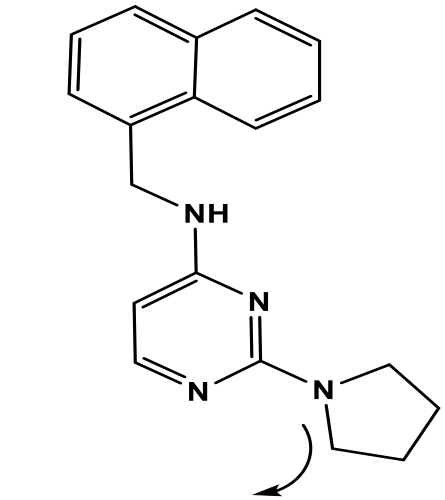


Fig2.2: Chemical structure of compounds (3–6) as anti-alzheimer's agent

Mohamed et al. designed, synthesised, analysed a series of 2,4-disubstituted pyrimidine derivatives as dual cholinesterase and Aβ -aggregation inhibitor. In vitro screening recognised N-(naphth-1ylmethyl)-2-(pyrrolidin-1-yl)pyrimidin-4-amine (compound 7a) as the most potent AChE inhibitor with IC50 value of 5.5μM. 2-(4-methylpiperidin-1-yl)-N-(naphth-1-ylmethyl)pyrimidin-4-amine (compound 7b) was observed as the most potent and selective BuChE inhibitor(selectivity index = 11.7) with IC50 value of 2.2 μM, and was about 5.7-fold more potent compared to the standard drug galanthamine(BuChE IC50 = 12.6 μM). N-benzyl-2-(4-methylpi perazin-1-yl)pyrimidin-4-amine(Compound 7c) also found to be the selective AChE inhibitor, exhibited good inhibition (59%) of hAChE-induced aggregation of Ab1–40 fibrils. SAR analysis demonstrate that the cholinesterase(ChEs) inhibition and selectivity were delicate to steric and electronic parameters at C-2 and C-4 positions of the central pyrimidine ring. The presence of pyrrolidine ring in 7a provided superior AChE inhibiton and BuChE inhibition (IC50 = 8.9 μM) relative to donepezil (BuChE IC50 = 12.6 μM). The presence of 4-methylpiperidine in 7b provided superior BuChE inhibitory potency and selectivity. Presence of N-benzyl and N-methylpiperazine in 7c provide good activity against AChE-induced aggregation of $A\beta_{1-40}$ peptides. These derivatives were non-toxic against the SH-Y5Y cell line. Therefore, 2,4-disubstituted pyrimidines could potentially serve as a suitable scaffold to develop ChEIs that possess anti-Ab aggregation activity and thus could target multiple pathological routes in AD.[73]

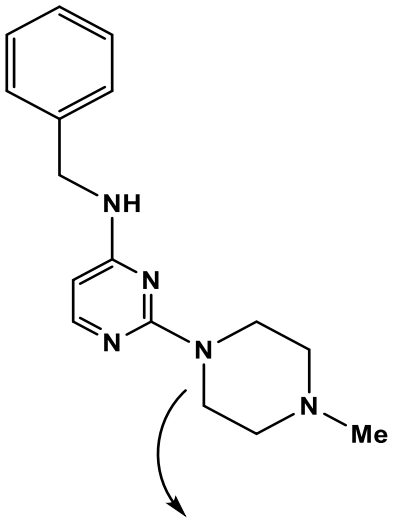
Mahgoub et al. designed, synthesised and biologically evaluated a series of thiazolo[3,2-a] pyrimidine bromide salt derivatives from 3,4-dihydropyrimidinethione precursors and observed In-vitro screening of all compounds as human acetylcholinesterase enzyme (hAChE) inhibitors via an Ellman-based colorimetric assay. These synthesised compounds 8a-d possessed great inhibition activities (better than 70%) at 10 μM, with IC50 value in the 1 μM range. Molecular docking stimulation confirmed that these synthesised derivatives resulted in strong binding to the peripheral anionic site(PAS) of the hAChE enzyme as compare to commercial drug tacrine and rivastigmine. Overall, these data suggested that thiazolo [3,2-a]

pyrimidines derivative provide a promising starting point to develop new AChE inhibitors against Alzheimer's disease.[74]



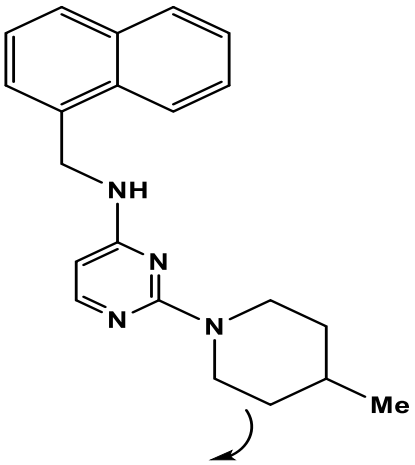
pyrrolidine ring enhances AChE inhibition

[7a]



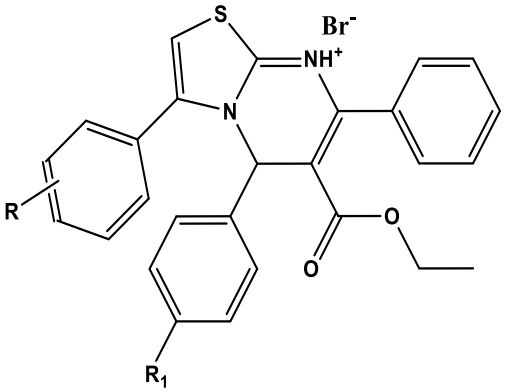
presence of N-benzyl and N-methyl piperazine enhance activity against aggregation of Aß$_{1-40}$fibrils

[7c]



presence of 4-methyl piperidine enhances BuChE inhibition

[7b]



8a, R_1=H, R=H **8 b, R_1=H, R=4OCH$_3$**
8c, R_1=H, R=F **8d, R_1=4OCH$_3$, R=H**

[8a-d]

Fig2.3: Chemical structure of compounds (7-8) as anti-alzheimer's agent

2.2 Structure–Activity Relationship of Pyrimidine Analogues:

Structure–activity relationship (SAR) serves as a guide for medicinal chemist to refine compounds into therapeutic relevance by optimising desired biological effects. In case of

Alzheimer's disease (AD), where multiple pathophysiology exists, so by SAR researchers can systematically refine molecules to boost selectivity, multitarget engagement, neuroprotection, efficacy, translational feasibility and safety. Pyrimidine derivatives referred as an ideal scaffold for SAR analysis because of its ability to hold multiple functional groups, adaptability, intrinsic biological compatibility. Analysis in past decades reveals that biological performance is mainly influenced by substituent positioning, electronic properties, molecular flexibility, and scaffold hybridization, rather than by the pyrimidine core alone. [75,76]

2.2.1 Influence of Core Pyrimidine Substitution on Neurodegeneration Inhibition

The pyrimidine ring have multiple sites for substitution, among which the C2, C4 and C6 positions play a crucial role in modulating receptor binding affinity, lipophilicity, and enzyme inhibitory activity. Example- Pyrimidine derivatives having amino or diamino group at C2 and C4 shows enhanced acetylcholinesterase (AChE) inhibition because these are polar in nature so due to favourable hydrogen bonding interactions within the enzyme's catalytic gorge.[77] SAR analysis shows increase in binding affinity without significantly increasing molecular weight, thereby preserving blood–brain barrier permeability. If polar groups replaced with hydrophobic substituents results in reduced enzyme interaction. This shows the necessity of polar substituents for effective binding.[78]

2.2.2 Aromatic Extension and Peripheral Anionic Site (PAS) Targeting

On introduction of aromatic or styryl moieties at particularly C5 or C6 position extend the molecular surface area, enabling π–π stacking interactions with aromatic residues thereby frequently enhance hydrophobic interactions with target proteins, resulting in increasing binding affinity and biological activity.. By this it shows multifunctionality as enhanced enzyme inhibition. SAR trends signify that electron-rich aromatic system improves PAS affinity, whereas excessive steric bulk minimise selectivity. However, aromatic extension allows pyrimidine derivatives to address AChE inhibition as well as beta amyloid aggregation. [79]

2.2.3 Role of Electron-Donating and Electron-Withdrawing Functional Groups

By introducing electron-donating groups such as methoxy or amino groups can significantly enhance antioxidant and neuroprotective properties whereas Electron-withdrawing substituents, like sulfonyl, carboxylate, and amide, can significantly impact binding stability and interaction perseverance. Phenylsulfonyl-pyrimidine carboxylate hybrids have this effect, where the combination of polar substituents enhances hydrogen bonding and electrostatic interactions with PAS residues. From SAR analysis, these groups modify pyrimidine derivatives from purely symptomatic agents to compounds with potential disease-modifying capability, particularly through amyloid aggregation inhibition. However, excessive polarity may negatively impact central nervous system exposure, therefore polarity control is required.[80]

2.2.4 Side Chain Flexibility and Blood–Brain Barrier Permeability

The introduction of flexible aliphatic side chains, such as oxoethyl or short alkyl amide linkers, plays a crucial role in upgrading pharmacokinetic behaviour. SAR analysis of 2-(2-oxoethyl) pyrimidine-5-carboxamide derivatives represents that moderate flexibility enhances blood–brain barrier penetration while maintaining acceptable enzyme

affinity.[81] Chains of limited length (two to three carbon units) appear ideal, whereas excessive chain length leads to conformational entropy penalties and subsided binding efficiency. This balanced chain length explains the developmental advantage of pyrimidine carboxamides over rigid natural alkaloids such as huperzine-A.[82]

2.2.5 Hybridization Strategy as a Multitarget SAR Driver

Hybridization of the pyrimidine scaffold with complementary pharmacophores illustrates one of the most significant SAR advancement in recent years. Amalgamation of morpholine, triazole, or coumarin moieties enhances multifunctionality of pyrimidine derivatives. Morpholine-containing hybrids improve aqueous solubility and CNS exposure, triazole units contribute to anti-inflammatory modulation, and coumarin or styryl components contribute to anti-amyloid activity. SAR analysis reveals that hybridization does not only add functionalities but reshapes molecular recognition, allowing a single compound to engage multiple relevant targets effectively.[83]

CHAPTER 3
THERAPEUTIC POTENTIAL OF PYRIMIDINE ANALOGUES

3.1 Pharmacological Significance of Pyrimidine Analogues

Pyrimidine Analogues shows significant importance in medicinal chemistry because of their wide range of pharmacological activities and therapeutic applications. Naturally occurring biomolecules contains pyrimidine nucleus such as cytosine, uracil, and thymine, which are essential components of nucleic acids. Due to their structural similarity with endogenous bases, pyrimidine derivatives exhibit good biological compatibility and strong interaction with different biological targets. Pyrimidine scaffolds exhibit several pharmacological activities such as anticancer, antibacterial, anti-inflammatory, antiviral, anticonvulsant, antioxidant, and neuroprotective effects. In neurodegenerative disorders, these compounds gained considerable attention because of their multi-target therapeutic action. Like, certain pyrimidine derivatives simultaneously act as acetylcholinesterase and monoamine oxidase inhibitors, thereby refining neurotransmitter levels and neuronal function. Some compounds also possess anti-inflammatory and antioxidant properties that may protect neurons from oxidative stress and inflammation-induced damage. Favourable pharmacokinetic properties such as low toxicity, metabolic stability, structural flexibility, and good blood–brain barrier penetration of pyrimidine analogues reveal another important advantages of pyrimidine analogues. These versatile properties make pyrimidine analogues as promising agents for development of novel therapeutic drugs against neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis. [61-68]

3.2 Therapeutic Mechanisms of Pyrimidine Analogues

3.2.1 Acetylcholinesterase Inhibition

One of the important therapeutic mechanisms of pyrimidine derivatives is Acetylcholinesterase Inhibition in neurodegenerative disorders. Acetylcholinesterase is an enzyme signifies a great role in breakdown of acetylcholine in the synaptic cleft. Therefore, Inhibition of this enzyme is must to increases acetylcholine concentration in the brain to improves cholinergic neurotransmission. In this regard, pyrimidine derivatives possessing significant acetylcholinesterase inhibitory activity that may help improve memory, cognitive function, and learning ability, particularly in Alzheimer's disease.[84]

3.2.2 Butyrylcholinesterase Inhibition

Butyrylcholinesterase Inhibition also plays an important role in improvement of cholinergic signaling. Activity of butyrylcholinesterase increases during progression of Alzheimer's disease and participates in acetylcholine degradation. Pyrimidine analogues, which inhibit butyrylcholinesterase, might improve cognitive performance and reduce progression of neurodegenerative symptoms.[85]

3.2.3 Monoamine Oxidase (MAO) Inhibition

Monoamine Oxidase Inhibition is an important approach for treatment of Parkinson's disease. Monoamine oxidase-B is involved in degradation of dopamine in brain. Pyrimidine derivatives which act as MAO-B inhibitors increase concentration of dopamine, thus improving motor function and preventing neurodegeneration in Parkinson's disease.[86]

3.2.4 Anti-Amyloid Activity

Anti-Amyloid Activity is necessary for preventing progression of Alzheimer's disease. Some pyrimidine analogues might inhibit formation and aggregation of beta-amyloid peptides that reduces formation of plaques and neuronal toxicity. This activity helps in enhancing neuronal communication and cognitive function.[87]

3.2.5 Anti-Tau Activity

Anti-Tau Activity involves inhibition of tau protein hyperphosphorylation and formation of neurofibrillary tangles. Abnormal aggregation of tau proteins interferes with functioning and structure of neurons in Alzheimer's disease. Pyrimidine derivatives with anti-tau activity might help prevent neurodegeneration.[88]

3.2.6 Antioxidant Activity

The Antioxidant Activity plays an extremely crucial role in neuroprotection. By virtue of their antioxidant activity, certain pyrimidine analogues can eliminate reactive oxygen species and protect neurons from the effects of oxidative stress-related damage. The antioxidant activity protects proteins, lipids, and nucleic acids within cells from oxidative damage.[89]

3.2.7 Anti-inflammatory Activity

Anti-inflammatory Activity can decrease inflammation associated with various neurodegenerative conditions. Specifically, some derivatives of pyrimidine act to decrease synthesis of pro-inflammatory cytokines such as TNF-α, IL-1β, and NF-κB. The inhibition of neuroinflammation can reduce damage to neurons and slow down the disease course**.[90]**

3.2.8 Neuroprotective Activity and Multiple Target Therapy

The Neuroprotective Activity is another significant feature of pyrimidine analogues. These substances can concurrently inhibit several pathological processes underlying neurodegeneration including oxidative stress, inflammation, neurotransmitter imbalance, mitochondria dysfunctions, and protein aggregation. Therefore, due to their multiple target action, pyrimidine analogues are promising candidates in the creation of potent anti-neurodegenerative drugs.[91]

3.3 Current Therapeutic Drugs and Their Limitations

Table1: Current Therapeutic Drugs and Their Limitations

Neurodegenerative Diseases	Traditional Drugs	Use	Limitations
Alzheimer's Disease	**Donepezil**	**Improves cognitive function and memory**	**Gastrointestinal disturbances, insomnia, bradycardia, symptomatic relief only**
Alzheimer's Disease	**Rivastigmine**	**Enhances cholinergic neurotransmission**	**Nausea, dizziness, vomiting, limited disease-modifying effect**
Alzheimer's Disease	**Galantamine**	**Improves cognition and neuronal signaling**	**short-term efficacy, Gastrointestinal side effects**
Alzheimer's Disease	**Memantine**	**Reduces excitotoxic neuronal damage**	**Headache, Confusion, limited effectiveness in severe stages**
Parkinson's Disease	**Levodopa**	**Dopamine replacement therapy**	**Motor fluctuations, Dyskinesia, reduced long-term efficacy**
Parkinson's Disease	Pramipexole	Improves motor symptoms	Hallucinations, sleep disorders, hypotension
Parkinson's Disease	Selegiline	Increases dopamine level	Insomnia, hypertensive interactions
Parkinson's Disease	Rasagiline	Slow down dopamine metabolism	Headache, dizziness, limited neuroprotection
Multiple Sclerosis	Teriflunomide	Reduces inflammatory progression	Teratogenicity, Hepatotoxicity, immunosuppression
Multiple Sclerosis	**Cladribine**	**Suppresses immune-mediated deterioration**	**Risk of infections, lymphopenia**

Multiple Sclerosis	**Dimethyl Fumarate**	**Reduces relapse frequency**	**Flushing, gastrointestinal disturbances**
Amyotrophic Lateral Sclerosis	**Riluzole**	**Slown down disease progression**	**Hepatotoxicity, limited survival benefit**
Amyotrophic Lateral Sclerosis	**Edaravone**	**Reduces oxidative neuronal damage**	**Limited efficacy, intravenous administration**
Huntington's Disease	**Tetrabenazine**	**Controls chorea and involuntary movement**	**Sedation depression, suicidal risk**
Huntington's Disease	**Deutetrabenazine**	**Improves motor symptoms**	**Drowsiness, psychiatric complications**

3.4 Research Gap

- Existing drugs mostly offers symptomatic relief, even don't modify the disease course.
- Only some compounds can simultaneously target AChE, BuChE, MAO-B, amyloid aggregation and oxidative stress.
- Insufficient studies on multitarget pyrimidine derivatives.
- Limited docking and SAR studies focused on multiple neurodegenerative targets.
- So, we need for novel pyrimidine scaffolds with better BBB permeability and lower toxicity.

3.5 Objectives

- Establishment of a virtual library of biologically active pyrimidine analogues effective against neurodegenerative disorders.
- Selection and preparation of neurodegenerative disease targets (MAO-B, AChE, BuChE, and other relevant proteins) using appropriate PDB structure.
- Evaluation of ligand–protein interactions through molecular docking studies.
- Identification of lead molecules exhibiting better binding affinity and validate their binding affinity using molecular dynamics simulations.
- Assessment of pharmacokinetic behaviour, drug-likeness, toxicity, and blood–brain barrier permeability through in silico ADMET analysis.

CHAPTER 4
EXPERIMENTAL WORK

4.1 In Silico Molecular Docking studies of Pyrimidine Derivatives

In this study, the pharmacological activity of pyrimidine analogs regarding potential targets associated with the development of neurodegenerative diseases, mainly Alzheimer's Disease, was analyzed by using computational approaches. In particular, the docking studies were performed in order to reveal binding affinity, interaction mechanism and possible inhibitory activity of the designed molecules toward selected target proteins.
Molecular docking analysis is a widely spread tool in computer-aided drug discovery and design to analyze interactions between receptors and ligands at the molecular level. It provides an opportunity to predict the preferred binding mode and the stability of complex formation between molecules. In this case, docking analysis was carried out by using several popular software packages (Schrödinger Suite and AutoDock, respectively).
The protein molecules used for docking analysis were downloaded from Protein Data Bank Database and subjected to necessary preparations prior to docking. These procedures involved removing water and ions, adding hydrogen atoms, establishing bond order, optimizing energy, etc. At the same time, ligand molecules were synthesized using suitable approaches, according to the type of the molecule. The prepared ligands were further docked to the target proteins.

Docking analysis was performed to determine the drugs having good binding affinities. This was done through analysis of the docking scores between potential drugs and proteins that cause the neurodegeneration. The best docking score will have a negative value. From the analysis of this study, useful information was generated on designing drugs against neurodegenerative diseases.

Table2: Docking Score and its interpretation

Glide Score	Interpretation
Around -3 to -5	Weak binding
Around -5 to -7	Moderate binding
Around -7 to -8	Good binding
Around -8 to -10	Very good/ strong binding

4.2 Selection criteria of proteins:

The current molecular docking simulation has been performed on four target proteins retrieved from the Protein Data Bank, including protein IDs such as 2BYB, 2OHP, 4BDT, and 6QAB. The selected proteins have been selected because of their critical involvement in causing major

neurodegenerative diseases, including Alzheimer's Disease and Parkinson's Disease. The selected target proteins predominantly involve the enzyme-based pathways that cause cholinergic dysfunction, thereby making it an important pharmaceutical target in neurodegeneration therapy.

The first selected protein, having the identifier ID as 2BYB, includes Monoamine Oxidase-B (MAO-B). This enzyme is involved in catalyzing the oxidation of dopamine, resulting in its depletion and generation of oxidative stress, both of which play vital roles in the pathogenesis of Parkinson's disease. The inhibition of MAO-B enzyme results in efficient therapy in treating neurodegenerative diseases.

The second selected protein identifiers, i.e., 2OHP and 4BDT, correspond to Acetylcholinesterase (AChE) enzymes that help in breaking down acetylcholine. Decreased concentrations of acetylcholine is one of the critical pathological events that occur in Alzheimer's disease, affecting cholinergic neurotransmission. Hence, inhibition of AChE enzymes increases cholinergic neurotransmission and is commonly used in anti-Alzheimer therapies.

ID 6QAB of protein is Butyrylcholinesterase (BuChE). It is another enzyme that is involved in acetylcholine metabolism and belongs to the group of cholinesterases. The action of BuChE has been noted to intensify at the advanced stages of Alzheimer’s disease; thus, it is regarded as a promising drug target in managing this condition.

For this reason, these proteins were chosen to be docked for assessing their interaction with the synthesized pyrimidines.

The selection of proteins for molecular docking is mainly dependent on the value of its resolution (Ångström, Å), which can be acquired from the X-ray crystallography data of the Protein Data Bank.
Higher resolution value means poorer protein structure quality which lead to lower accuracy in docking

Table3: X ray crystallographic resolution of proteins from PDB bank and its interpretation

Resolution (Å)	Structure quality
< 1.5 Å	Excellent
1.5-2.5 Å	Very good / acceptable for docking
> 3 Å	Lower accuracy

Proteins with a resolution close to 2 Å are considered ideal for molecular docking due to the following characteristics:

- high-quality atomic coordinates,
- active site conformation, and
- higher accuracy of ligand interaction.

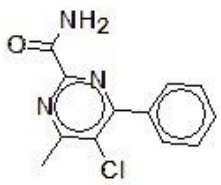
Table4: PDB ID used

PDB ID	Protein/ Enzyme name	Enzyme type	Associated disease
2BYB	Monoamine oxidase -B(MAO-B)	Oxidoreductase enzyme	Parkinsons disease and also linked to Alzheimer
2OHP	Acetylcholinesterase	Cholinesterase	Alzheimer Disease
4BDT	Acetylcholinesterase (AChE)	Cholinesterase	Alzheimer Disease
6QAB	Butyrylcholinesterase (BuChE)	Cholinesterase	Alzheimer Disease

4.3 Software used

1. Protein data bank (PDB)
2. AutoDockTools-1.5.7
3. Chem Draw ultra 7.0.4
4. Discovery Studio 2025 Client
5. OpenBabel-2.4.1
6. Schrodinger

4.4 Established Structures of Compounds used in Molecular Docking



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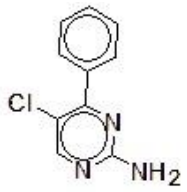

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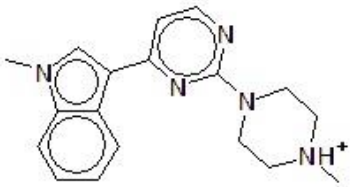

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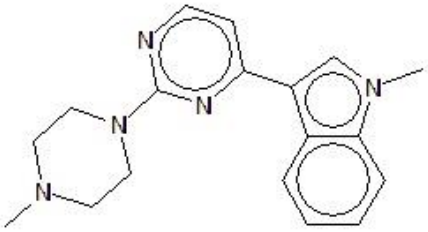

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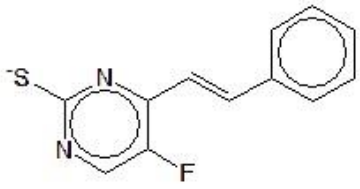

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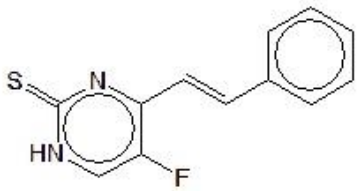

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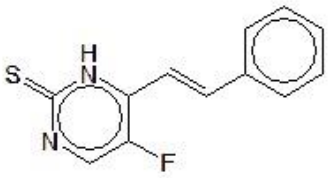

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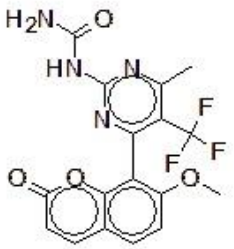

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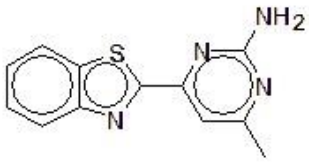
8



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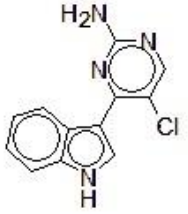

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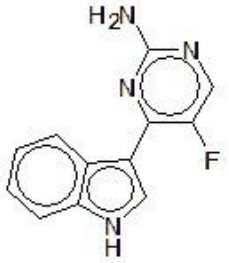

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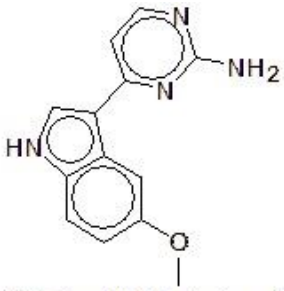

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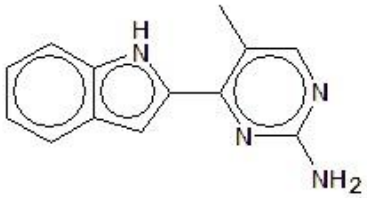

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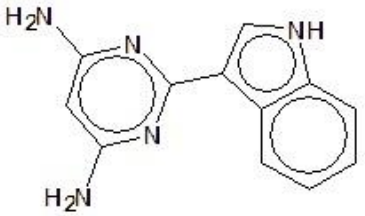

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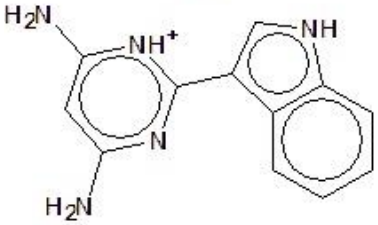

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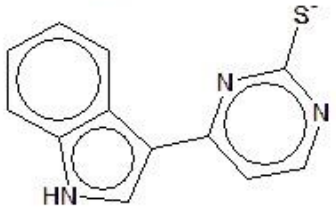

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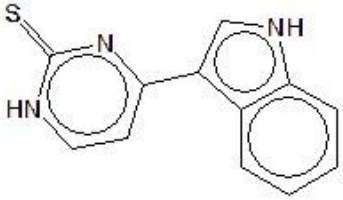

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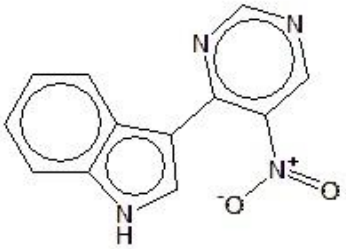

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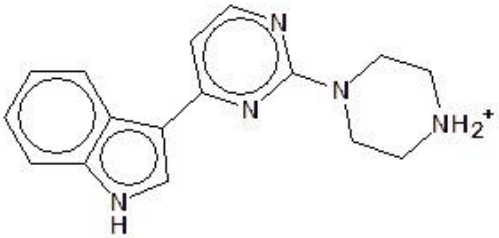

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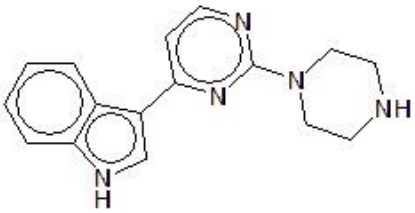

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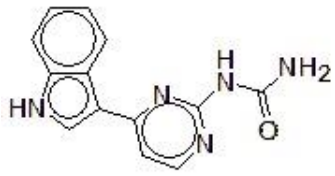
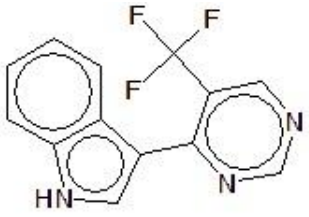


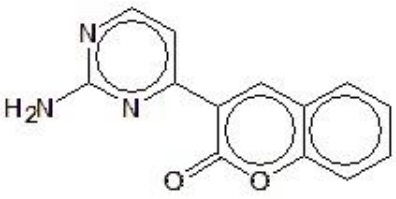
NC(=O)Nc1nccc(-c2c[nH]c3ccccc23)n1

21



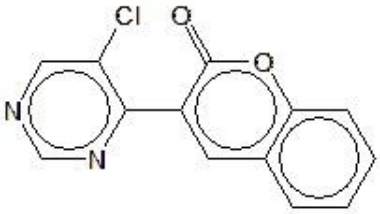
FC(F)(F)c1cncnc1-c1c[nH]c2ccccc12

22



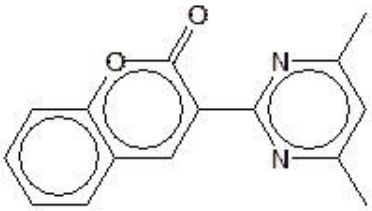
Nc1nccc(-c2cc3ccccc3oc2=O)n1

23



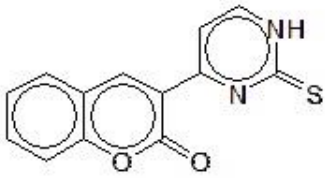
O=c1oc2ccccc2cc1-c1ncncc1Cl

24



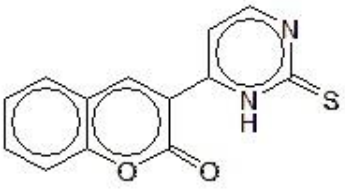
Cc1cc(C)nc(-c2cc3ccccc3oc2=O)n1

25



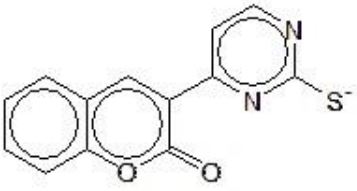
O=c1oc2ccccc2cc1-c1cc[nH]c(=S)n1

26



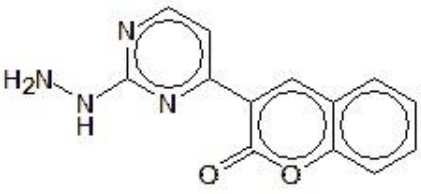
O=c1oc2ccccc2cc1-c1ccnc(=S)[nH]1

27



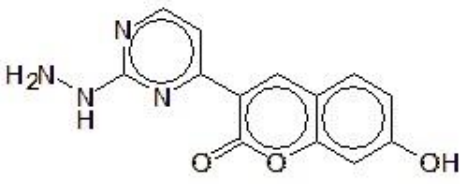
O=c1oc2ccccc2cc1-c1ccnc([S-])n1

28



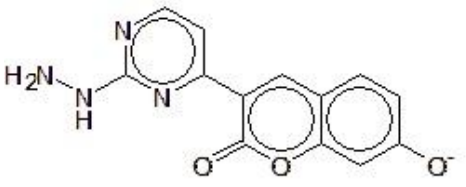
NNc1nccc(-c2cc3ccccc3oc2=O)n1

29



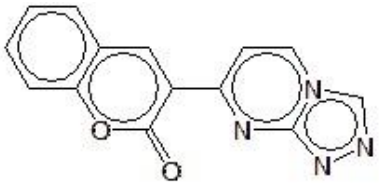
NNc1nccc(-c2cc3ccc(O)cc3oc2=O)n1

30



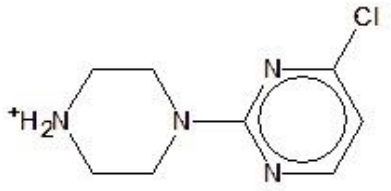
NNc1nccc(-c2cc3ccc([O-])cc3oc2=O)n1

31



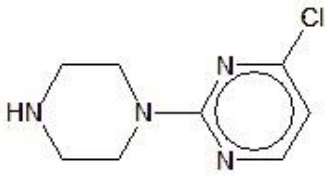
O=c1oc2ccccc2cc1-c1ccn2cnnc2n1

32



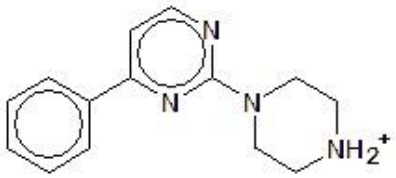
Clc1ccnc(N2CC[NH2+]CC2)n1

33



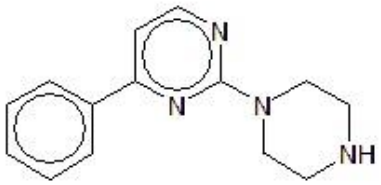
Clc1ccnc(N2CCNCC2)n1

34



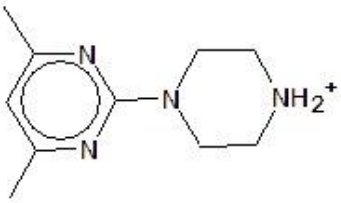
c1ccc(-c2ccnc(N3CC[NH2+]CC3)n2)cc1

35



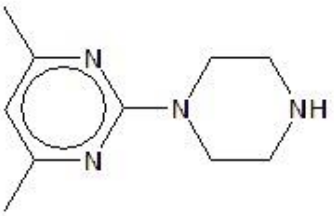
c1ccc(-c2ccnc(N3CCNCC3)n2)cc1

36



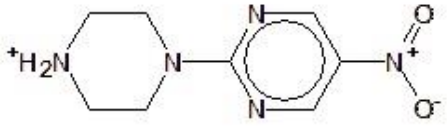
Cc1cc(C)nc(N2CC[NH2+]CC2)n1

37



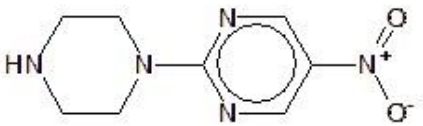
Cc1cc(C)nc(N2CCNCC2)n1

38



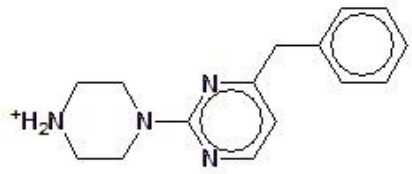
O=[N+]([O-])c1cnc(N2CC[NH2+]CC2)nc1

39



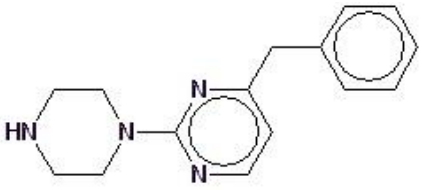
O=[N+]([O-])c1cnc(N2CCNCC2)nc1

40



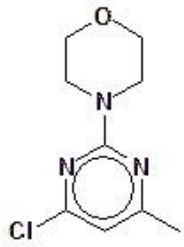
c1ccc(Cc2ccnc(N3CC[NH2+]CC3)n2)cc1

41



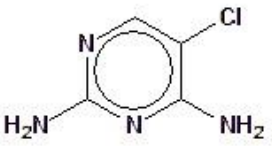
c1ccc(Cc2ccnc(N3CCNCC3)n2)cc1

42



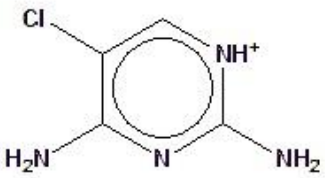
Cc1cc(Cl)nc(N2CCOCC2)n1

43



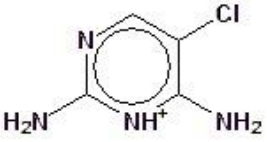
Nc1ncc(Cl)c(N)n1

44



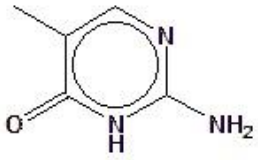
Nc1nc(N)c(Cl)c[nH+]1

45



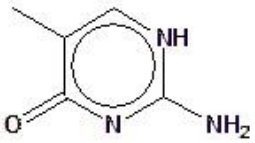
Nc1ncc(Cl)c(N)[nH+]1

46



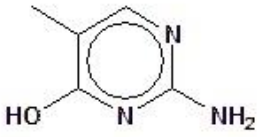
Cc1cnc(N)[nH]c1=O

47



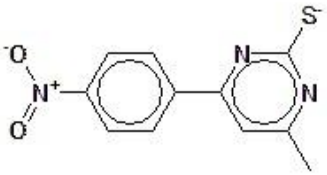
Cc1c[nH]c(N)nc1=O

48



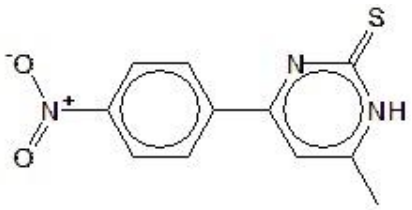
Cc1cnc(N)nc1O

49



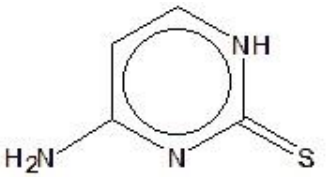
Cc1cc(-c2ccc([N+](=O)[O-])cc2)nc([S-])n1

50



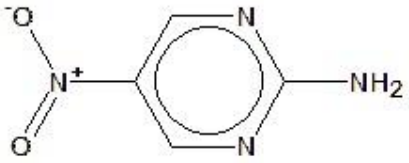
Cc1cc(-c2ccc([N+](=O)[O-])cc2)nc(=S)[nH]1

51



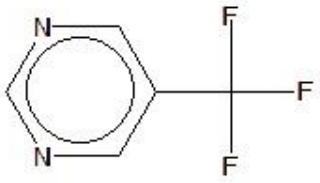
Nc1cc[nH]c(=S)n1

52



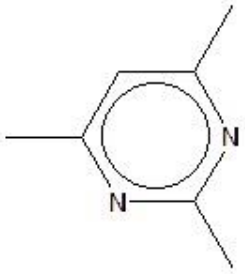
Nc1ncc([N+](=O)[O-])cn1

53



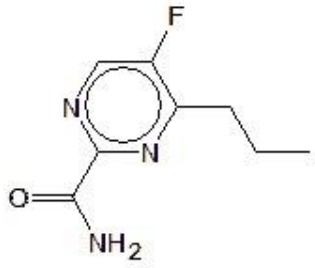
FC(F)(F)c1cncnc1

54



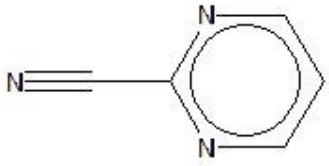
Cc1cc(C)nc(C)n1

55



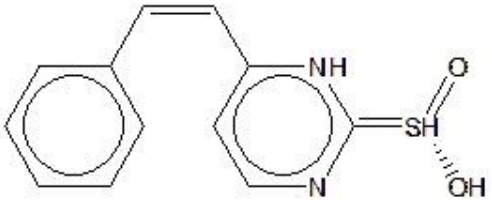
CCCc1nc(C(N)=O)ncc1F

56



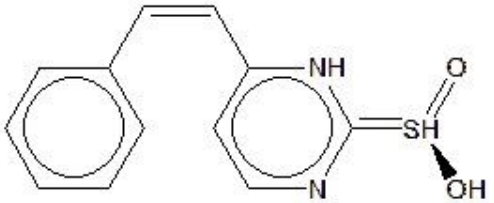
N#Cc1ncccn1

57



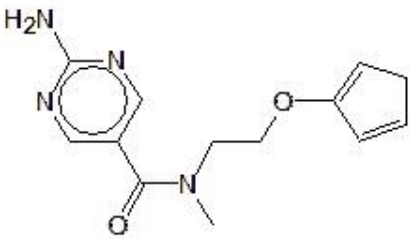
O=[S@H](O)=c1nccc(/C=C\c2ccccc2)[nH]1

58



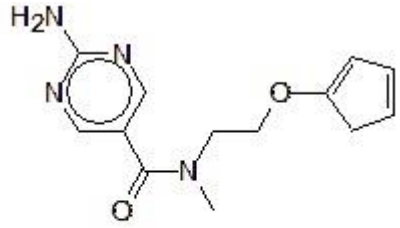
O=[S@@H](O)=c1nccc(/C=C\c2ccccc2)[nH]1

59



CN(CCOC1=CCC=C1)C(=O)c1cnc(N)nc1

60



CN(CCOC1=CC=CC1)C(=O)c1cnc(N)nc1

61

4.5 Observation Table:

Table 5: Observed docking score

S No.	SMILE	Docking Score_2BYB	Docking Score_2OHP	Docking Score_4BDT	Docking Score_6QAB
1	Cc1nc(C(N)=O)nc(-c2ccccc2)c1Cl	-8.84145	-3.84078	-8.84145	-7.53601
2	Nc1ncc(Cl)c(-c2ccccc2)n1	-7.99221	-3.87824	-7.99221	-6.17075
3	Cn1cc(-c2ccnc(N3CC[NH+](C)CC3)n2)c2ccccc21	-4.4388	-4.49973	-4.4388	-5.3241
4	CN1CCN(c2nccc(-c3cn(C)c4ccccc34)n2)CC1	-3.46641	-2.51155	-3.46641	-5.01913
5	Fc1cnc([S-])nc1/C=C/c1ccccc1	-6.26978	-2.94061	-6.26978	-5.80401
6	Fc1c[nH]c(=S)nc1/C=C/c1ccccc1	-7.27313	-2.90562	-7.27313	-6.02506
7	Fc1cnc(=S)[nH]c1/C=C/c1ccccc1	-7.47005	-2.44888	-7.47005	-5.76529
8	COc1ccc2ccc(=O)oc2c1-c1nc(NC(N)=O)nc(C)c1C(F)(F)F	-7.59853	-4.0862	-7.59853	-6.52142
9	Cc1cc(-c2nc3ccccc3s2)nc(N)n1	-7.68101	-4.48038	-7.68101	-6.62549
10	Nc1ncc(Cl)c(-c2c[nH]c3ccccc23)n1	-10.3604	-4.83747	-10.3604	-6.45812
11	Nc1ncc(F)c(-c2c[nH]c3ccccc23)n1	-9.55882	-3.96996	-9.55882	-6.70102
12	COc1ccc2[nH]cc(-c3ccnc(N)n3)c2c1	-8.21717	-4.14915	-8.21717	-5.86257

13	Cc1cnc(N)nc1-c1cc2ccccc2[nH]1	-8.09718	-4.50841	-8.09718	-6.5431
14	Nc1cc(N)nc(-c2c[nH]c3ccccc23)n1	-7.77718	-3.7675	-7.77718	-8.00379
15	Nc1cc(N)[nH+]c(-c2c[nH]c3ccccc23)n1	-7.6225	-1.66053	-7.6225	-3.34503
16	[S-]c1nccc(-c2c[nH]c3ccccc23)n1	-6.61965	-3.61048	-6.61965	-6.7244
17	S=c1nc(-c2c[nH]c3ccccc23)cc[nH]1	-9.68599	-3.17427	-9.68599	-7.45984
18	O=[N+]([O-])c1cncnc1-c1c[nH]c2ccccc12	-9.59449	-3.78572	-9.59449	-7.16455
19	c1ccc2c(-c3ccnc(N4CC[NH2+]CC4)n3)c[nH]c2c1	-10.8706	-4.71706	-10.8706	-8.63713
20	c1ccc2c(-c3ccnc(N4CCNCC4)n3)c[nH]c2c1	-7.76032	-3.38352	-7.76032	-6.02949
21	NC(=O)Nc1nccc(-c2c[nH]c3ccccc23)n1	-9.33003	-5.11784	-9.33003	-7.8924
22	FC(F)(F)c1cncnc1-c1c[nH]c2ccccc12	-10.7105	-4.62629	-10.7105	-8.38402
23	Nc1nccc(-c2cc3ccccc3oc2=O)n1	-9.15805	-4.26796	-9.15805	-6.80998
24	O=c1oc2ccccc2cc1-c1ncncc1Cl	-8.19932	-2.95516	-8.19932	-6.93239
25	Cc1cc(C)nc(-c2cc3ccccc3oc2=O)n1	-7.54867	-2.71101	-7.54867	-7.4932
26	O=c1oc2ccccc2cc1-c1cc[nH]c(=S)n1	-8.79554	-3.34887	-8.79554	-6.54861
27	O=c1oc2ccccc2cc1-c1ccnc(=S)[nH]1	-8.00391	-2.72932	-8.00391	-6.20874
28	O=c1oc2ccccc2cc1-c1ccnc([S-])n1	-6.29062	-1.74204	-6.29062	-4.77253
29	NNc1nccc(-c2cc3ccccc3oc2=O)n1	-8.38446	-4.61939	-8.38446	-7.64065
30	NNc1nccc(-c2cc3ccc(O)cc3oc2=O)n1	-9.40212	-4.5186	-9.40212	-6.92372

31	NNc1nccc(-c2cc3ccc([O-])cc3oc2=O)n1	-6.74673	-1.39285	-6.74673	-4.11493
32	O=c1oc2ccccc2cc1-c1ccn2cnnc2n1	-8.17062	-2.33104	-8.17062	-6.3165
33	Clc1ccnc(N2CC[NH2+]CC2)n1	-5.86996	-3.68369	-5.86996	-6.61374
34	Clc1ccnc(N2CCNCC2)n1	-4.03154	-1.55799	-4.03154	-3.62176
35	c1ccc(-c2ccnc(N3CC[NH2+]CC3)n2)cc1	-5.39605	-4.11458	-5.39605	-8.43147
36	c1ccc(-c2ccnc(N3CCNCC3)n2)cc1	-7.12327	-1.82572	-7.12327	-5.4392
37	Cc1cc(C)nc(N2CC[NH2+]CC2)n1	-5.95203	-3.70965	-5.95203	-6.18587
38	Cc1cc(C)nc(N2CCNCC2)n1	-2.96198	-1.45424	-2.96198	-3.22584
39	O=[N+]([O-])c1cnc(N2CC[NH2+]CC2)nc1	-3.94927	-3.56477	-3.94927	-1.25727
40	O=[N+]([O-])c1cnc(N2CCNCC2)nc1	-3.04723	-0.824255	-3.04723	-2.00452
41	c1ccc(Cc2ccnc(N3CC[NH2+]CC3)n2)cc1	-7.36433	-4.50172	-7.36433	-7.66035
42	c1ccc(Cc2ccnc(N3CCNCC3)n2)cc1	-7.28275	-2.30103	-7.28275	-5.91878
43	Cc1cc(Cl)nc(N2CCOCC2)n1	-5.50293	-3.41756	-5.50293	-5.0056
44	Nc1ncc(Cl)c(N)n1	-4.8066	-2.93567	-4.8066	-4.3513
45	Nc1nc(N)c(Cl)c[nH+]1	-2.56198	-1.3403	-2.56198	-3.29741
46	Nc1ncc(Cl)c(N)[nH+]1	-3.3148	-0.633406	-3.3148	-2.1541
47	Cc1cnc(N)[nH]c1=O	-5.02871	-3.48099	-5.02871	-4.18379
48	Cc1c[nH]c(N)nc1=O	-3.06354	-2.3767	-3.06354	-2.75131
49	Cc1cnc(N)nc1O	-2.25827	-1.41624	-2.25827	-1.92725
50	Cc1cc(-c2ccc([N+](=O)[O-])cc2)nc([S-])n1	-5.15862	-2.73658	-5.15862	-4.21273
51	Cc1cc(-c2ccc([N+](=O)[O-])cc2)nc(=S)[nH]1	-6.37621	-1.61862	-6.37621	-4.81117

52	Nc1cc[nH]c(=S)n1	-5.65255	-4.03965	-5.65255	-5.90666
53	Nc1ncc([N+](=O)[O-])cn1	-3.57308	-2.93203	-3.57308	-3.30088
54	FC(F)(F)c1cncnc1	-5.66861	-3.2428	-5.66861	-4.96509
55	Cc1cc(C)nc(C)n1	-5.0481	-2.63482	-5.0481	-4.17549
56	CCCc1nc(C(N)=O)ncc1F	-7.44084	-4.49703	-7.44084	-5.5839
57	N#Cc1ncccn1	-4.61489	-3.21303	-4.61489	-4.16951
58	O=[S@H](O)=c1nccc(/C=C\c2ccccc2)[nH]1	-6.87711	-4.52071	-6.87711	-6.87329
59	O=[S@@H](O)=c1nccc(/C=C\c2ccccc2)[nH]1	-8.89433	-4.61034	-8.89433	-6.12776
60	CN(CCOC1=CCC=C1)C(=O)c1cnc(N)nc1	-7.04941	-3.12577	-7.04941	-6.39444
61	CN(CCOC1=CC=CC1)C(=O)c1cnc(N)nc1	-6.12016	-2.38494	-6.12016	-6.54182

CHAPTER 5
RESULT AND ANALYSIS

Molecular docking simulation was performed on selected pyrimidine derivatives with respect to four target proteins, 2BYB, 2OHP, 4BDT, and 6QAB, using molecular docking simulation software. Docking scores of the selected ligand-protein complexes are provided in the docking table. Docking score is one of the vital parameters that determine the binding affinity between the ligand and receptor proteins. Higher docking score value means a better binding interaction and stable ligand-receptor complex.

Many of the screened compounds had high docking scores, especially against protein 2BYB and 4BDT. Those compounds that had docking scores above −10 kcal/mol indicated better binding affinity toward the target proteins and thus considered as potential drug candidates for neurodegenerative disease.

Compounds having serial numbers 10, 19, and 22 had the best docking scores against proteins 2BYB and 4BDT. Serial number 19 showed the maximum docking score of about −10.87 kcal/mol, whereas serial number 22 showed a docking score of about −10.71 kcal/mol. Serial number 10 also had an excellent docking score of around −10.36 kcal/mol. This indicates good binding interaction with the receptor proteins' active site.

Some of the factors responsible for increased binding affinity of these compounds include certain physical and chemical properties available in the structure of the pyrimidines. In the selected compounds, there are aromatic and heteroaromatic fused ring structures that enable strong hydrophobic and π-π stacking interactions with aromatic amino acids present in the active sites of the proteins. These interactions contribute significantly to the stability of the ligand-protein interaction complex.

Further, compounds having amino (-NH_2), amide, or nitrogen-heterocyclic structures are capable of forming strong hydrogen bonds with active site amino acids. The formation of hydrogen bonds is important for increasing ligand-binding affinity. The presence of electron-withdrawing groups like chloro (Cl), fluoro (F), and trifluoromethyl [-CF_3] substituent groups in some of the compounds resulted in improved docking scores.

5.1Analysis of Interaction diagrams

5.1.1.1 Interaction Analysis of Compound 19 with protein 2BYB (MAO-B):

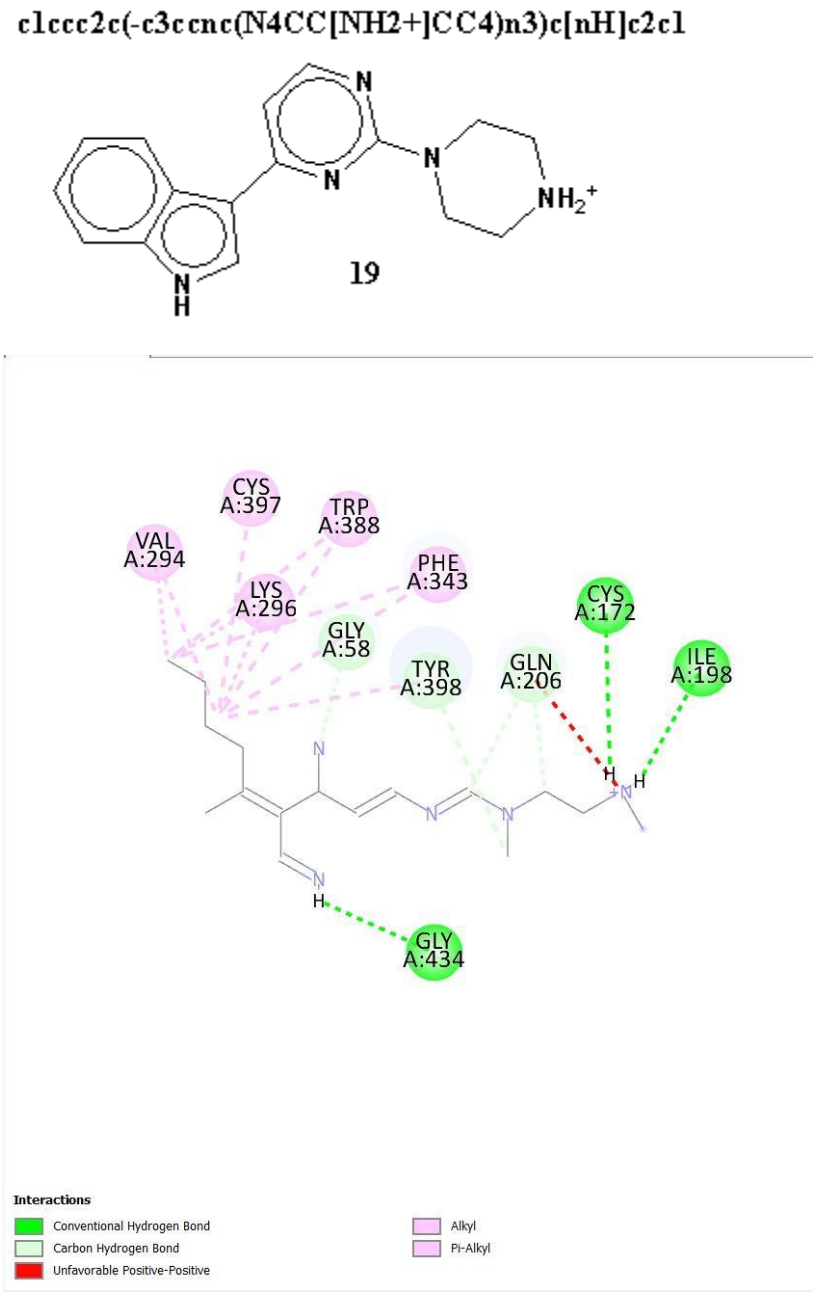


Fig5.1: Interaction of Compound 19 with protein 2BYB (MAO-B)

In the case of compound 19, a good docking score with protein 2BYB was observed having docking energy of −10.87 kcal/mol, suggesting that the compound formed a stable ligand-receptor complex with significant binding affinity.

An interaction diagram of this compound illustrated various types of hydrogen bonds, carbon hydrogen bonds, alkyl interactions, and π-alkyl interactions that occurred between the ligand and receptor.

Conventional hydrogen bond interactions were formed between the ligand and Gly434, Cys172, and Ile198 residue of the receptor protein, providing stabilization to the ligand within the binding pocket. Hydrogen bonding interactions play an important role in keeping proper orientation of the ligand and improving receptor binding activity. Additionally, carbon

hydrogen bond interactions were made with residues Gly58, Tyr398, and Gln206, helping in improving ligand-receptor binding.

Alkyl and π-alkyl hydrophobic interactions were also found between residues Val294, Lys296, Trp388, Phe343, and Cys397. Various hydrophobic interactions increase van der Waals interaction and stabilizes the ligand aromatic ring structure. Due to a fusion of aromatic rings within compound 19, π-π and hydrophobic interactions can be easily formed with aromatic amino acids of the receptor.

Since there is more than one nitrogen heterocycle in the ligand's chemical structure, it has extra hydrogen bond donors and acceptors, thus enhancing its interaction ability with the active site residues. Though one interaction in nature was not favorable, that is, between the positive charge on residue Gln206 and that of compound 19, all other interactions were extremely favorable because there were too many.

Consequently, the excellent docking score of compound 19 could be credited to:

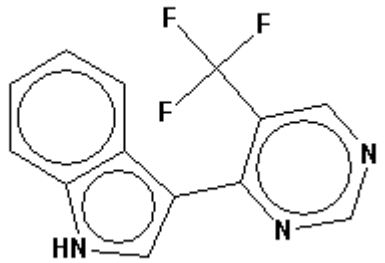
- Multiple hydrogen bonds
- Excellent hydrophobic and π-alkyl interactions
- Fused aromatic heterocycles in the molecule
- Good fitting inside the active site
- More conjugation and better binding

From the above interactions, it can be said that compound 19 is a strong inhibitor for Monoamine Oxidase B (MAO-B).

5.1.2Interaction analysis of compound 22 with 2BYB (MAO-B):

FC(F)(F)c1cncnc1-c1c[nH]c2ccccc12

22



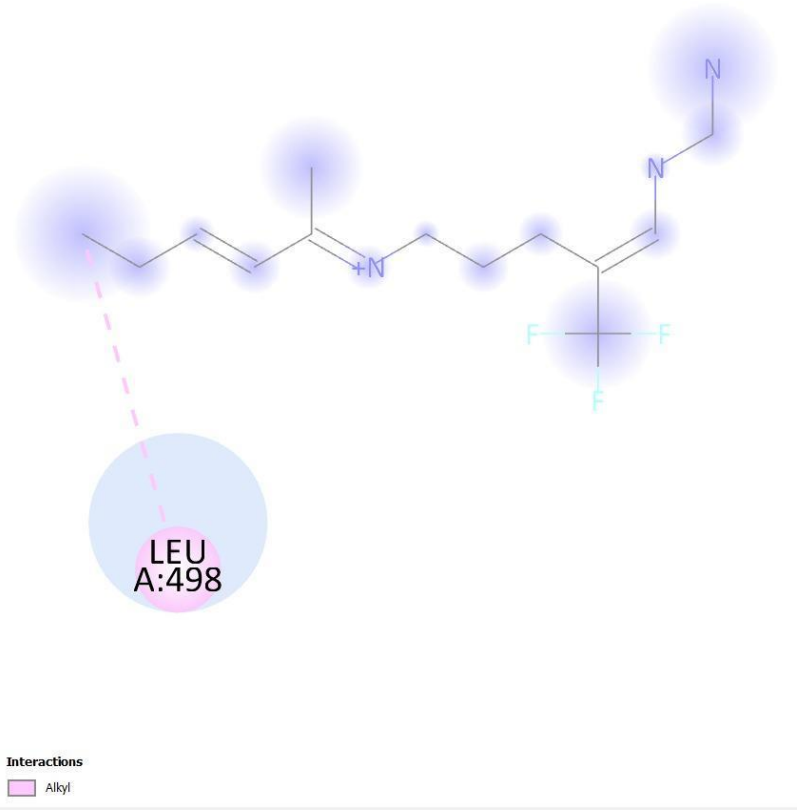


Fig5.2: Interaction of compound 22 with 2BYB (MAO-B)

Compound 22 had a high docking score of about −10.71 kcal/mol with protein 2BYB. This indicated the ability to form favorable binding interactions with the receptor protein. Compound 22 interacted via hydrophobic interactions with the amino acid residue Leu498.
There was a notable alkyl interaction that occurred between the hydrophobic part of the ligand and the Leu498 residue of the protein. Due to the presence of the trifluoromethyl group, the ligand's lipophilicity and hydrophobic surfaces were increased leading to high hydrophobic interactions. Hydrophobic interactions assist in stabilizing ligand-protein complexes as well as enhancing docking affinity.
The aromatic pyrimidine ring of the ligand also made the molecule more planar to enable appropriate fitting in the receptor's pocket. Additionally, the conjugation effect increased the van der Waals interaction of the molecule with the hydrophobic part of the protein. Electron withdrawing effect from the fluorine groups in the trifluoromethyl moiety of the ligand could have improved its electron density distribution.
Although the hydrogen bond interactions of compound 22 were less compared to those of compound 19, compound 22 had very good hydrophobic interaction and steric complementarity. These factors largely influenced the ligand's high docking score.
It is believed that the high binding affinity of compound 22 can be due to the following factors:

- Trifluoromethyl group (-CF_3)
- Hydrophobic effects
- Aromatic heterocycle moiety fused together
- Increased lipophilicity of the molecule

- Steric accommodation within the active site cavity

5.1.3Interaction analysis of compound 10 with 4BDT (acetylcholinesterase)

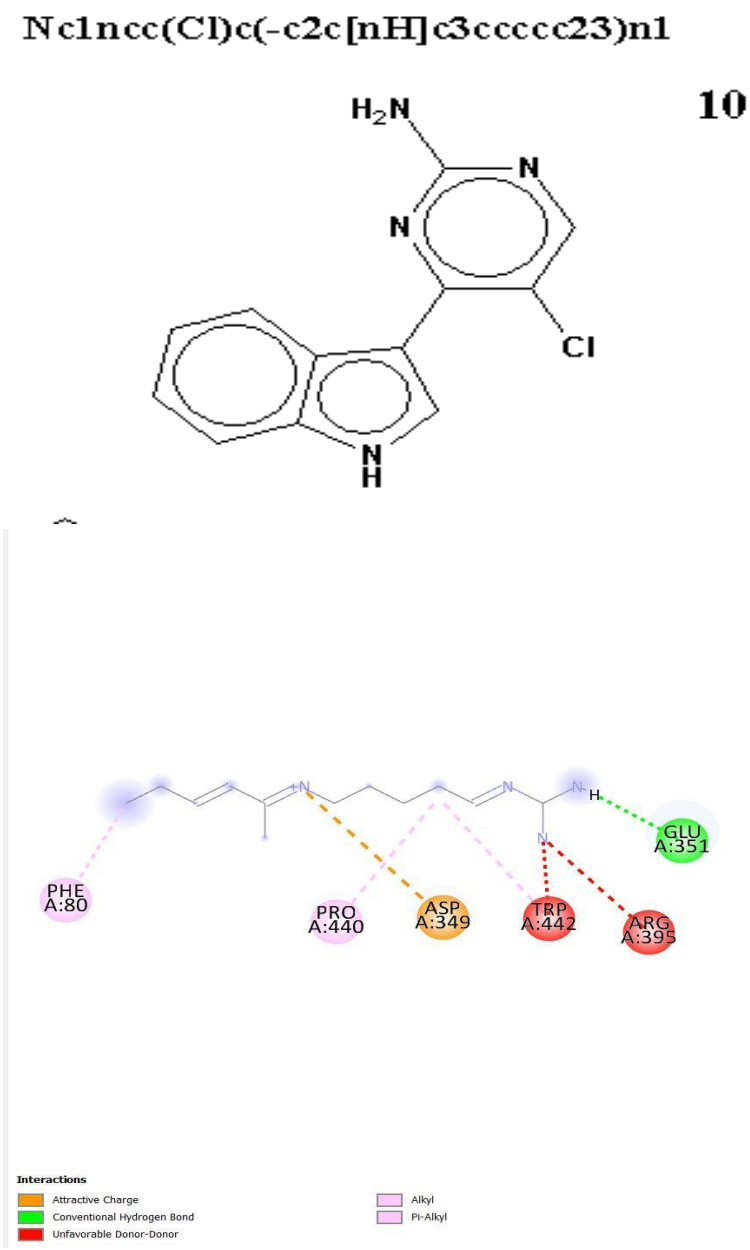


Fig5.3: Interaction of compound 10 with 4BDT (acetylcholinesterase)

Compound 10 showed a very good docking score of −10.36 kcal/mol on protein 4BDT, showing strong binding properties and ligand–protein complex formation with Acetylcholinesterase. According to the interaction pattern, there were many hydrophobic interactions, hydrogen bonding, and electrostatic interactions that contributed towards formation of the ligand–protein complex.

Firstly, there was a hydrogen bond interaction with residue Glu351 in which the hydrogen bond plays a vital role in stabilizing the ligand within the active site pocket. Furthermore, hydrogen

bonds help in stabilizing the ligand within the binding pocket by maintaining the correct orientation. Electrostatic attractive charge interaction was noted with Asp349 residue that shows the attraction of charges between ligand and receptor. An attractive charge interaction shows positive charges on the nitrogen atom and negative charges on the side chain of the amino acid residue. This is helpful in stabilizing the complex.

Hydrophobic interactions such as alkyl interaction were noted with residues Phe80 and Pro440. Hydrophobic interactions are important in forming hydrophobic bonds in the binding pocket. These interactions help in stabilizing the ligand within the receptor. The heterocyclic aromatic system of the ligand helps in forming such hydrophobic interactions.

There was also π–alkyl interaction with Trp442, which is a significant aromatic amino acid present in the active site region of the protein. Aromatic interactions of such kind significantly contribute in increasing the affinity and stability of heterocyclic structures inside the receptor pocket.

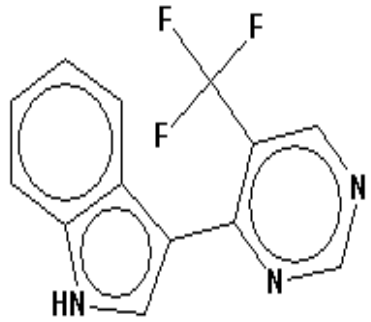
While unfavorable donor-donor interactions were seen with Trp442 and Arg395 residues, the overall binding profile remained very favorable due to dominating stabilizing interactions over destabilizing interactions. The nitrogen containing heterocyclic structure in molecule 10 offers multiple interaction sites, hence enhancing the binding property of the receptor.

The good docking score of molecule 10 can thus be attributed to the following factors:

- Presence of conventional hydrogen bonding with Glu351
- Electrostatic interactions with Asp349
- Hydrophobic and π-alkyl interactions
- Aromatic and heterocyclic pyrimidine structure
- Proper steric complementarity within the active site gorge of Acetylcholinesterase

5.1.4Interaction analysis of compound 22 with 4BDT (acetylcholinesterase)

FC(F)(F)c1cncnc1-c1c[nH]c2ccccc12



22

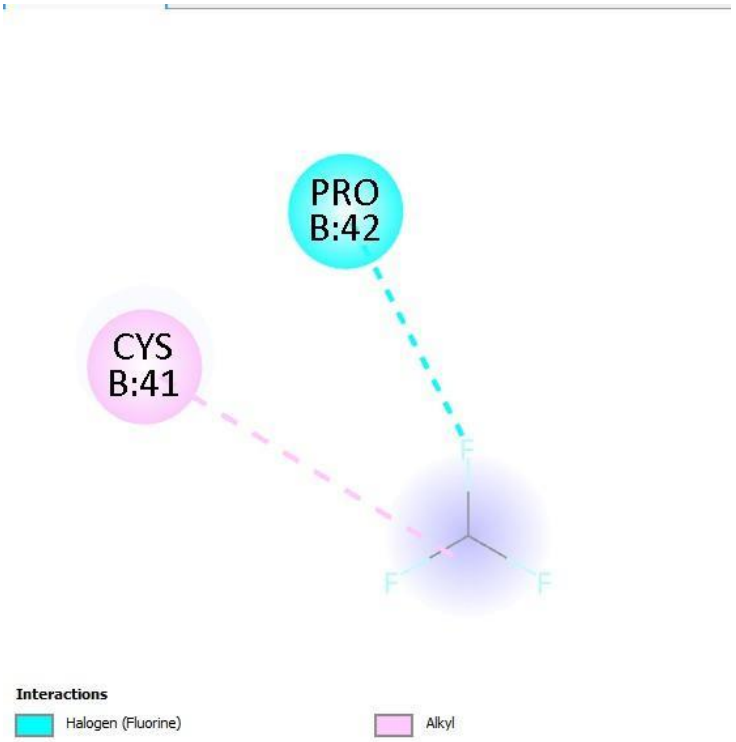


Fig5.4: Interaction of compound 22 with 4BDT (acetylcholinesterase)

Compound 22 was found to have a docking score of about −10.71 kcal/mol when docked into protein 4BDT, which shows that it has high binding affinity towards the Acetylcholinesterase protein. Hydrophobic interactions and halogen interactions were identified as key interactions that help stabilize the ligand-protein complex in the active site of the receptor protein.

Hydrophobic interactions were noted between the ligand and residue Cys41 through an alkyl interaction, suggesting that there is favorable interaction between the nonpolar part of the ligand and the hydrophobic amino acid residue in the binding pocket. Hydrophobic interactions are important for the stability of the ligand in the receptor cavity.

The ligand had significant halogen interactions with the residue Pro42 via the trifluoromethyl (CF3) group. Halogen interactions play an important role in docking studies since they are known to enhance binding specificity and ligand-receptor interaction. Fluorine atoms increase the lipophilic nature of the ligand by contributing more to van der Waals interactions with other residues.

Trifluoromethyl group present in compound 22 contributes greatly towards improved docking. Electronegative fluoride groups affect the electron distribution of the ligand and increase the hydrophobic nature. This helps in achieving better interactions with the hydrophobic part of the receptor protein. Moreover, the aromatic nature of the pyrimidine ring structure plays an important role in achieving proper steric complementarity as well as optimal accommodation within the active site cavity of Acetylcholinesterase enzyme.

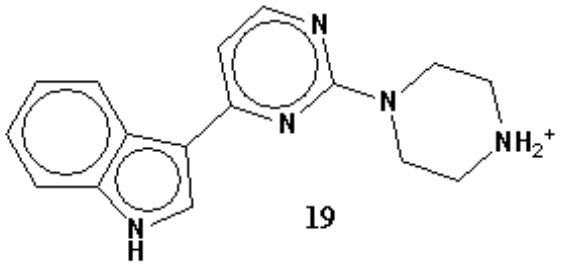
While there was relatively few hydrogen bond interactions between the ligand and the target molecule, the hydrophobic and halogen interactions proved to be sufficient to yield a very good docking score. This clearly demonstrates the importance of hydrophobic and halogen-based interactions in the binding mode of compound 22 with the target protein.

Thus, the highly favorable binding affinity of compound 22 can be attributed to:

- Presence of trifluoromethyl (–CF_3) group
- Strong hydrophobic interaction with Cys41 residue
- Halogen interaction of fluorine atoms with Pro42 residue
- High lipophilicity of the molecule
- Stable accommodation within the active site cavity of Acetylcholinesterase

5.1.5Interaction Analysis of compound 19 with 6QAB (butyrylcholinesterase):

c1ccc2c(-c3ccnc(N4CC[NH2+]CC4)n3)c[nH]c2c1



19

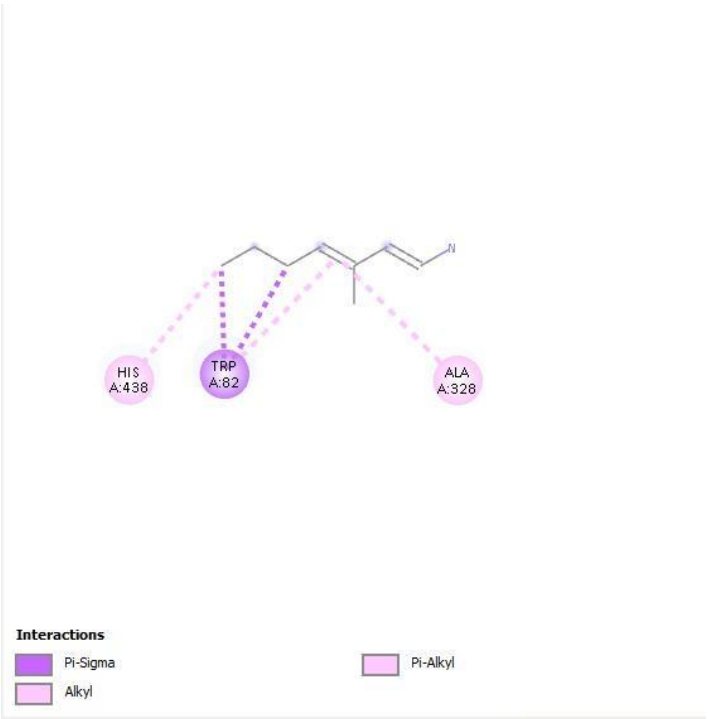


Fig5.5: Interaction of compound 19 with 6QAB (butyrylcholinesterase)

Compound 19 showed a relatively high docking score for protein 6QAB, showing strong binding affinity towards the Butyrylcholinesterase enzyme. In the interaction study, it was found that the ligand was highly stabilized by hydrophobic interaction including alkyl, π-alkyl, and π-sigma interactions in the binding site of the protein receptor.
Hydrophobic alkyl interactions were formed between amino acid residues His438 and Ala328 of the receptor protein. These interactions indicate strong hydrophobic interactions between

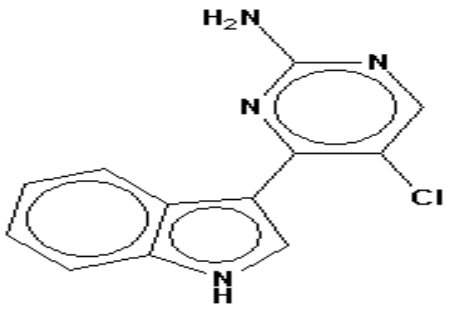
the ligand and the hydrophobic pocket of the protein molecule. Hydrophobic interactions play a significant role in ligand stability and enhancing the affinity of the protein-ligand complex. A π-sigma interaction was also seen in the case of the amino acid residue Trp82. This interaction is seen when the aromatic π-electrons in the heterocyclic aromatic structure of the ligand interact with the sigma bond present in the residue. These interactions help stabilize the aromatic ligand in hydrophobic sites and increase the binding potential.
Also, π-Alkyl interactions are seen between residue Trp82. Alkyl interactions are the interactions between the aromatic ring system of the ligand and the alkyl group of the amino acid. The presence of fused aromatic and conjugated heterocyclic groups in compound 19 facilitates these interactions.
The aromatic pyrimidine framework and conjugated nature of the ligand make the molecule flat and allow it to fit perfectly into the active site pocket of Butyrylcholinesterase. Nitrogen-containing heterocyclic moieties also provide stability and recognition for the formation of receptor affinity.

Thus, the good docking score obtained by compound 19 for protein 6QAB could be explained by:

- Presence of strong hydrophobic alkyl interactions
- Possibility of π-σ interaction with Trp82
- Formation of π-alkyl interactions in the active site
- Aromatic heterocyclic ring system in the structure
- Conjugation and planarity of the molecule
- Accommodation in the receptor binding pocket

5.1.6Interaction analysis of compound 10 with protein 6QAB (butyrylcholinesterase)

Nc1ncc(Cl)c(-c2c[nH]c3ccccc23)n1



10

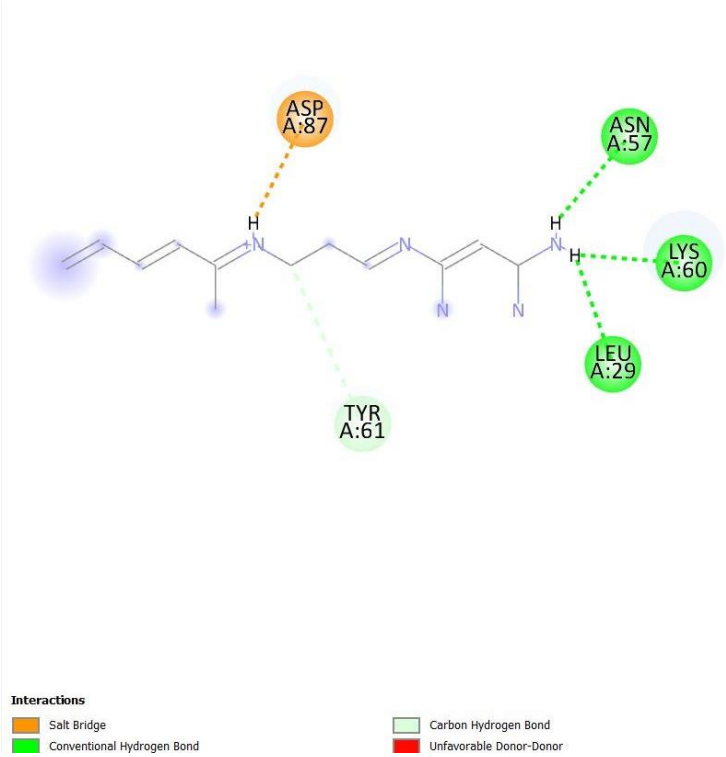


Fig5.6: Interaction of compound 10 with protein 6QAB (butyrylcholinesterase)

Compound 10 showed a significant docking score for protein 6QAB, indicating that there were favorable interactions towards Butyrylcholinesterase. Interaction study showed that compound 10 interacts through a number of conventional hydrogen bonds, carbon hydrogen bonds and electrostatic interactions with the receptor protein inside the active site area. Ligand shows conventional hydrogen bonds interaction with amino acid residues Asn57, Lys60, and Leu29. Conventional hydrogen bonds interactions contribute significantly to the stabilization of the complex by keeping the ligand at the proper orientation inside the active site pocket. Hydrogen bonds facilitate proper binding of the ligand inside the active site area. Carbon hydrogen bonds interaction was observed with residue Tyr61. Carbon hydrogen bonds interactions are relatively less stable than conventional hydrogen bonds but still improve the binding stability of the ligand inside the active site pocket.
An important salt bridge interaction was observed with amino acid residue Asp87. Salt bridge interactions refer to the electrostatic interactions between positively charged amino acids residues and the negatively charged functional group in the ligand. Electrostatic interactions increase ligand binding ability inside the active site pocket. Pyrimidine derivatives show protonated nitrogen atom inside the molecule that favors this type of electrostatic interactions. The heterocyclic nitrogen-based pyrimidine skeleton in compound 10 increases the interaction possibilities due to the presence of hydrogen bond donors and acceptors. Moreover, the aromatic structure plays a crucial role in the stabilization of the compound, which ensures its correct orientation inside the active site pocket of the protein.

The docking score of compound 10 with respect to protein 6QAB can thus be explained by:

- Hydrogen bonding interactions
- Carbon-hydrogen bonding with Tyr61

- Salt bridge interaction with Asp87
- Heterocyclic nitrogen-based pyrimidine scaffold
- Molecular stability and receptor pocket accommodation

In conclusion, the interaction pattern of compound 10 demonstrates its good inhibitory potential against Butyrylcholinesterase (BuChE), a relevant target for treatment of Alzheimer's disease. These results demonstrate good receptor binding properties and the promise of using compound 10 in future studies on anti-Alzheimer drugs.

5.1.7 Poor Interaction profiles of pyrimidine derivatives with protein 2OHP:

It was determined through docking simulation studies that all synthesized compounds exhibited comparatively poor docking affinities towards protein target 2OHP when compared with other target proteins like 2BYB, 4BDT, and 6QAB. The docking affinities of ligands for protein 2OHP were mostly found to lie in the range of −1 to −5 kcal/mol.
Such reduced docking affinities of the ligands might be due to structural attributes associated with the protein 2OHP. The active site of 2OHP protein might lack favorable steric as well as electronic compatibility for accommodating the bulky fused aromatic pyrimidine derivatives. Moreover, it might lack favorable amino acid residues for establishing proper hydrogen bonding, hydrophobic interaction, and π-π stacking interactions which are necessary for the binding of the ligand.
Since all of the synthesized compounds have aromatic/heterocyclic rings which tend to favor hydrophobic interaction; it might be possible that the hydrophobicity of the active site of 2OHP is too less to stabilize the ligand. Moreover, the improper orientation of the ligand along with non-complementarity with respect to the receptor might further contribute to reduced docking affinity towards the targeted receptor.

CHAPTER 6
FUTURE PROSPECTS, CONCLUSION & SOCIAL IMPACTS

6.1 Future prospects

As per this present molecular docking study, pyrimidine derivatives show promising potential as therapeutic agents against neurodegenerative disease-related protein targets. A number of compounds have been found to bind efficiently with MAO-B, AChE, and BuChE enzymes. Their potential application as drug molecules against Alzheimer's Disease and Parkinson's Disease cannot be overlooked on account of such findings. Though the above docking results seem promising, yet the computational data requires further investigation via experiments to substantiate it. Future research studies may involve in vitro enzyme inhibition studies, in silico cell line-based testing, toxicity assessments, and even in vivo pharmacological studies to investigate the efficiency and safety of these compounds.

Further structural modifications in the promising pyrimidine derivatives may further refine their binding potential as well as their selectivity and other pharmacokinetic properties. The incorporation of certain functional groups along with modification in aromatic substituents would prove beneficial in this regard. Some advanced in silico techniques such as molecular dynamics, ADMET, QSAR modeling, and free energy calculations may further assist in the comprehensive evaluation of their binding with receptors.Optimization of structure of the potential pyrimidine analogues could lead to improved ligand-binding ability and selective pharmacological properties. Functionalization of the molecule and alteration of the aromatic rings could help in achieving effective binding to the receptors. Various advanced methods like molecular dynamics studies, ADMET studies, QSAR analysis, and free energy calculations can be applied to analyze the protein-ligand binding.

The current study will thus serve as an excellent basis for the development of new pyrimidine-based drugs against neurodegenerative diseases.

6.2 Conclusion

Neurodegenerative disorders continue to constitute some of the most complicated and difficult-to-treat medical conditions. Due to the lack of success in the action of currently used monotherapy targeting individual disease-related pathways, there is a need for development of multi-target approaches to the disease management. In this regard, pyrimidine derivatives can be considered as promising agents owing to the good BBB penetration, synthetic flexibility, and multi-target interaction capability. SAR analysis allowed concluding that the substitutions at the C-2, C-4, C-5, and C-6 sites play a critical role in defining the strength of enzyme inhibition, specificity of receptor affinity, and neuroactivity of the molecules. It was found that electron-donating amino groups enhance the AChE inhibition through hydrogen bonding inside the catalytic gorge, whereas aromatic substituents at C-5 allow for the

interaction of the compounds with peripheral anionic site and amyloid-beta protein through π–π stacking. Combining the pyrimidine nucleus with other pharmacophore fragments further increases the multi-target capability of the designed inhibitors. Docking analysis performed on the MAO-B (2BYB), AChE (4BDT), and BuChE (6QAB) targets showed that Compounds 19 and 22 have defined binding patterns on the MAO-B target, while Compounds 10 and 22 show good interactions with AChE. Compound 19 and 10 had significant binding capacity to the BuChE active site. In summary, the findings reported above have provided an interesting set of pyrimidine analogues with actual multi-target inhibition properties for all the three investigated enzymes. Of course, since the results were derived from a computer-based study, there is still need for experimental confirmation. However, these results have established a sound basis on which to design new pyrimidines for neuroprotection in the future. Hopefully, the present study would act as a valuable starting point in the quest for drug discovery against such neurodegenerative diseases as Alzheimer's disease and Parkinson's disease.

6.3 Social Impacts

Neurodegenerative diseases like Alzheimer's and Parkinson's are super tough challenges globally, especially with aging populations. Not only do these conditions mess with a person's mental and physical abilities, but they also really hit hard emotionally, socially, and financially for families, caregivers, and health systems. So, finding new treatments that target crucial enzymes involved in these illnesses would be hugely beneficial. Recently, researchers looked into pyrimidine derivatives, which showed they could bind well to MAO-B, AChE, and BuChE enzymes that play major roles in neurodegenerative diseases. This could help create better treatments to boost cognitive functions, slow down disease progress, and make life easier for folks dealing with these conditions. Also, using computational methods like molecular docking saves a lot on costs and time compared to lab tests, letting scientists zoom through possible drug options faster. Eventually, creating cheap and effective drugs from pyrimidine derivatives might lower health costs, help patients more, and support older folks as well.

So, this study helps more than just science; it tackles a big global health issue that heavily affects both society and the economy too.

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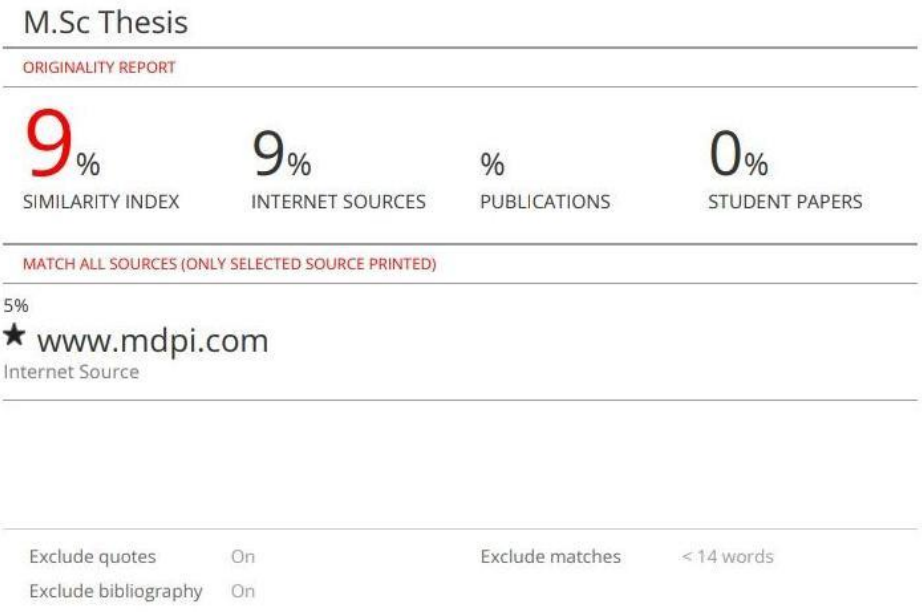

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