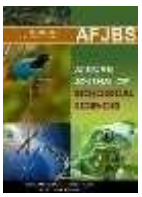
https://doi.org/10.48047/AFJBS.6.3.2024.345-357

African Journal of Biological Sciences



A review of an alzheimer's disease and pharmacological activity of heterocyclic derivatives for ad management

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Article History
Volume 6, Issue 3, May 2024
Received: 12 Apr 2024
Accepted: 15 May 2024
Doi:10.48047/AFJBS.6.3.2024.345-357

Abstract
The brain disease category includes Alzheimer's disease, which is brought on by the destruction of brain nerve cells. The neurons that are necessary for cognitive function and normal human functioning are the first to suffer damage in Alzheimer's disease. Memory, verbal, and cognitive issues were all new to the affected person; the brain alterations that produce them are believed to start 20 years or more before symptoms appear. The influence of Alzheimer's disease on public health is discussed in this article, along with its prevalence and incidence, mortality and morbidity, care usage, expenses, and overall effect on family carers. The particular focus for examining the patient's journey from awareness of cognitive modification to potential treatment with a course of drugs that change the core biology of Alzheimer's. Currently, only a few authorized drug classes, including N-methyl-d-aspartate antagonists and cholinesterase enzyme inhibitors, are available to treat illness. Only the symptoms of AD may be effectively treated with these drugs; the illness is neither cured nor prevented by them. We aim to investigate potent therapies capable of reversing or ameliorating AD. The main goal of this review is to study the pathophysiology, pharmacological action, and treatment of Alzheimer's disease. Furthermore, heterocyclic compounds are the fundamental building blocks for novel pharmaceuticals.

Key words: Alzheimer's disease, Neurons, cholinesterase enzyme, heterocyclic molecules.

INTRODUCTION

Alzheimer's disease affects 6.5 million adults 65 and older globally. More than 70% of them are 75 years or older. Worldwide, dementia affects about 55 million individuals, and Alzheimer's disease is thought to be involved in 60 to 70 per cent of cases. The initial indication of the illness manifests in the loss of past meetings or events, culminating in significant memory challenges and a diminishing ability to perform daily tasks. Drugs may hasten the progression of symptoms. The programs and services may be helpful to AD patients and their caretakers.[1]

Disorientation is a symptom of Alzheimer's dementia, a degenerative brain condition. Modifications in the brain are characteristic, and these changes typically result in protein deposition. Brain shrinkage brought on by the illness results in the loss of brain cells. The

condition progresses, beginning with mild memory loss and possibly escalating to losing communication and environmental awareness skills. These changes can make it difficult for a person to function. Alzheimer's disease typically affects areas of the brain that control the brain's essential responsive function, which has a substantial impact on an individual's knack for managing the routines of everyday life.

Although there are drugs that can treat the symptoms, there is presently no cure for Alzheimer's disease [2]. This evaluation aims to give a comprehensive overview of the pathology, causes, diagnosis, and therapies for Alzheimer's disease. Concentrating on several pathogenic pathways, such as the aggregation and misfolding of A and tau, inflammation, oxidative damage, and others, draws attention to the ongoing research being done on medications that may be able to prevent or treat AD. When brain function is severely lost, it can lead to complications, including infection, starvation, or dehydration, all of which might be fatal. Scientists are still unsure of the exact causes of Alzheimer's disease [3]. Several factors are at play, and each may affect a person differently.

- The first identified associated risk factor for Alzheimer's disease is age.
- Decades before the first signs show, the brain may change.
- Researchers are examining the possible links between environment, food, education, and Alzheimer's disease development.[4]. Figure .1 shows healthy and Alzheimer's-affected brain

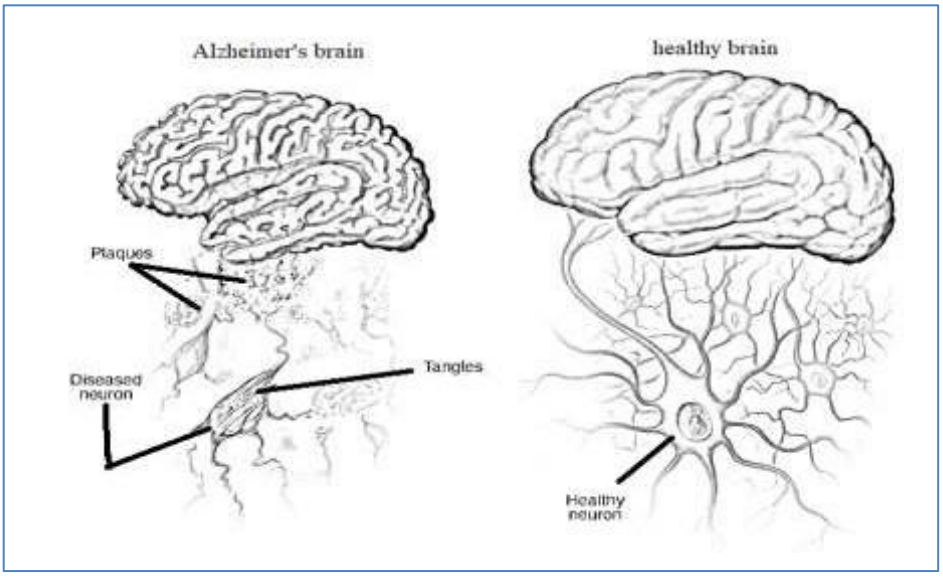

Fig. 1 shows a healthy brain and an Alzheimer's-affected brain.

Signs:

One of the earliest indicators of dementia like Alzheimer's disease is often memory issues. Beyond memory concerns, signs of Alzheimer's disease might encompass a constellation of the subsequent symptoms are :1). Having trouble handling money and paying bills 2) Reduced or poor judgment; difficulty carrying out ordinary tasks at home, at work, or for amusement 3). Losing stuff and being unable to follow previous procedures to locate them 4) Modifications in personality, conduct, or mood. Every five years, the number of persons over 65 with the disease condition may rise, and 14 million are predicted to be impacted by it by 2060. The risk increases with age, and symptoms may not appear until age 60. Giving care has advantages for both the caregiver and the person receiving it. It could include some personal sacrifice on the part of the carer, such as the satisfaction of helping a friend or relative, and it might result in the growth of new skills and interpersonal connections. Even though the majority of individuals are enthusiastic

about caring for their family and friends, caring for an individual with Alzheimer's disease at home can present considerable challenges, often reaching a point of overwhelming complexity.

Symptoms [5]:
One of the early warning indications of Alzheimer's disease, which is recognized for its memory loss symptoms, is having trouble recalling recent conversations or occurrences. Memory loss and other symptoms, however, become worse as the illness gets worse.

Memory:
Alzheimer's disease-related forgetfulness lasts longer and gets shoddier, while everyone periodically experiences memory loss. One's ability to perform daily duties at home or work steadily declines due to memory loss. It is more challenging to concentrate and reason while dealing with abstract concepts like numbers and multitasking due to the cognitive impairment caused by Alzheimer's disease. It might be challenging to manage your money, maintain your cheque books in balance, and pay your bills on time.

Making decisions and judgments:
When someone has Alzheimer's disease, their ability to do so under normal circumstances is reduced. For instance, a person might choose unwisely in social situations or choose improper clothing for the weather. It might become more difficult for someone to respond to routine issues, making them forget to deal with things like decisions while driving or handling food on the stove that is burning.

Changes in personality and conduct:
In addition to affecting emotions and behaviors, changes in brain function brought on by Alzheimer's disease may also cause the following issues [6]: loss of interest in activities, social disengagement, mood fluctuations, a loss of trust in others, aggression or anger, Alterations in sleep patterns, a loss of self-control, and deceptions.

Retained abilities:
People with Alzheimer's disease can still maintain some cognitive ability, even as their symptoms get worse. Reading or listening to books, telling tales, sharing experiences, singing, listening to dances, playing instruments, drawing, or performing crafts are just a few examples of abilities that could be kept. Speak with your doctor if you have concerns about your memory or other cognitive functions. If a family member or friend's thinking upsets you, discuss your worries, obtain their perspective, and then go to the doctor with them.

Causes:
The precise causation of Alzheimer's disease is unknown. Brain proteins don't function as naturally as they ought to, though. The neurons eventually die because of the scratching, which causes them to lose their connections. Several diseases can cause memory loss and other dementia symptoms, some of which are curable. The disorder is caused by specific genetic anomalies less than 1% of the time, and people with these abnormalities almost always get the sickness. In such cases, the sickness often shows symptoms in middle age. The memory-controlling portion of the brain is typically the first to suffer damage, and the disease often advances for years before any symptoms appear. The death of neurons occurs in other areas of the brain predictably. The brain

has drastically shrunk by the time the condition is fully developed. Researchers looking into the origins of Alzheimer's disease are examining two proteins:

• Sculptures: The protein beta-amyloid is a fragment of a more considerable protein that clumps together and appears to have harmful effects on neurons and disrupt brain cell communication. These clusters manifest as amyloid plaques, which are more considerable deposits that also contain other cellular waste.

• Twists: Tau proteins change shape and group together to form neurofibrillary tangles in AD. The tangles disrupt the transport system, which also damages the cells.[7]

Alzheimer's disease pathology:

Additionally, playing a significant role in the pathophysiology of AD is oxidative stress. When oxidative damage is induced, free radicals like hydrogen peroxide (H_2O_2), the reactive oxygen species (ROS) or hydroxyl (OH), and superoxide (O_2) are formed. Due to this damage, DNA strands are broken, the cell membrane's nucleic acids and sugars are destroyed, and the cell dies [8,9]. The pathophysiology of AD is mainly caused by the APP (amyloid precursor protein) lane, which produces amyloid peptides [10]. As per the amyloid precursor protein theory, when α or β-secretase cleaves APP, it releases inevitable byproducts. While the products resulting from β-secretase cleavage are generally deemed harmless, the process itself is a fundamental aspect of this theory; β-secretase is involved in dividing the APP pathway that leads to amyloid genesis and non-amyloid genesis. The synthesis of C-terminal APP occurs during the cleavage of β-secretase. Depending on the cleavage location, peptides of different lengths are produced from the plasma membrane by γ-secretase. A-42 is the most prominent pathogenic contributor to AD among these peptides [11,12]. Amyloid beta (A) peptides aggregate and reactive oxygen species (ROS) are produced; this leads to the development of senile plaques, which is the pathophysiology of AD [13]. Several additional investigations have shown that an inflammatory process contributes to the pathophysiology of AD. The Schematic path way of Pathology of AD are shown in figure 2. Histopathological research has revealed a correlation between the existence of A peptides in Alzheimer's disease patients and the aggregation of active microglial cells alongside inflammatory substances. These include complementing elements such as acute-phase responses and anti-inflammatory cytokines [14]. Several studies have shown that AD is caused by genetic variations in cytokines, particularly the over expression of interleukin-1 and acute phase proteins [15,16,17]. Based on epidemiologic studies, it has been hypothesized that long-term anti-inflammatory drug use may slow or stop the progression of AD [18, 19].

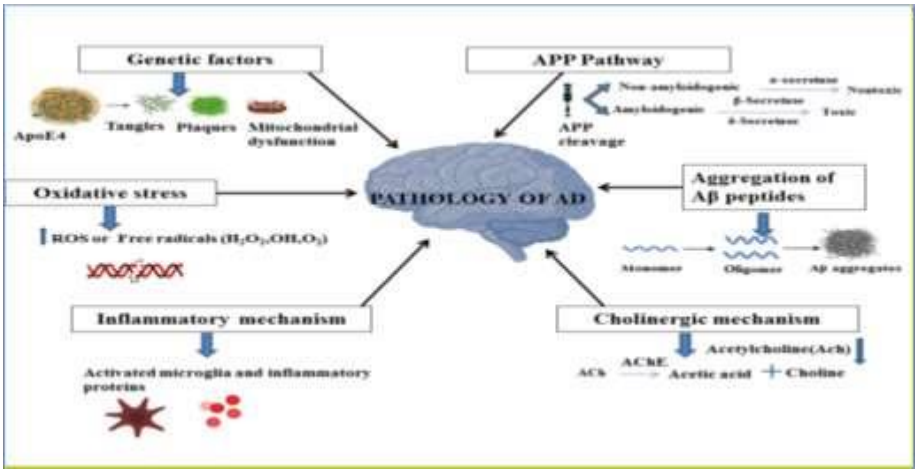

Fig.2 Schematic path way of Pathology of AD

Disease development and onset:

Preclinical, moderate cognitive impairment (MCI), and dementia phases are all included in a helpful paradigm developed by the National Institute on Ageing and the Alzheimer's Association (NIA-AA). Various measures are employed to evaluate the symptoms and pathological advancement of Alzheimer's disease [21]. Specific biomarkers indicating the emergence of neuropathological patterns associated with AD, even without signs or symptoms, distinguish the preclinical stage [22]. A paradigm developed by the NIA-AA working group describes three substages of this stage as the gradual buildup of amyloidosis, neurodegeneration, and modestly declining cognitive function [23]. However, cognitive deficits are observed in memory, verbal language, attention, visuospatial abilities, and executive function [24]. Diagnosing Mild Cognitive Impairment (MCI), mainly that induced by Alzheimer's Disease (AD), can be bolstered by specific markers. These include challenges predominantly in memory, a gradual decline in cognitive faculties over an extended period (spanning months to years), the absence of Parkinson's disease and hallucinations, a lack of cerebrovascular risk factors, and the absence of behavioral or language impairments. [25]. It is possible to categorize AD as moderate or severe once it has advanced to the dementia stage; moderate AD leads to difficulties recognizing family members and friends, increased memory loss, and apparent behavioral abnormalities. This phase often leads to life-threatening situations, necessitating full-time care for the individual. Depending on when the disease is diagnosed, the prognosis for Alzheimer's disease can differ, but the average life expectancy from the time of diagnosis typically ranges between 3 to 10 years [26]. The ongoing expectation is one of progressive neurodegeneration that persists until the individual's passing.

Diagnosis:

Before pinpointing Alzheimer's dementia, the patient needs to fulfil the requirements for a general diagnosis of dementia. These requirements include that the patient must have cognitive impairment, show indicators of neuropsychiatric symptoms that interfere with their ability to do their work or interact with others, demonstrate a decrease from their former condition, and not be accounted for by delirium or another mental disease (using information about the patient's and an informant's medical history, an objective cognitive evaluation, and the presence of impairment in two or more of the following areas: language function, typical personality or conduct, information acquisition, and memory [27].

Treatment:

Several therapeutic approaches can decrease the disease's progression and improve the quality of life for sufferers. In addition to increasing cognitive function and lowering the risk of AD, maintaining cardiovascular fitness [28], engaging in mental activity [29], and consuming plant-based diets [30] are all beneficial. However, genetic susceptibility to AD is thought to have a higher influence on the start of the disorder [31]. In the realm of pharmacology, there exist two treatments for these conditions: N-methyl D-aspartate (NMDA) receptor antagonists, which hinder glutamate interaction with NMDA receptors to prevent neuronal overactivity and cell demise, and acetylcholinesterase inhibitors, which impede the enzymatic breakdown of acetylcholine [33], are two classes of approved medications that can be used to treat AD symptoms. Memantine is the sole NMDA receptor antagonist, but rivastigmine, donepezil, and galantamine are approved AchE

inhibitors. This focus is driven by the current limitations of available medications, which cannot treat or prevent the onset of the condition effectively [34]. Two of these medications, Aducanumab and Lecanemab, have received FDA approval to treat AD and early AD, respectively. These medications frequently contain monoclonal antibodies that attack A. During clinical studies, both of these drugs slightly slowed the rate of cognitive decline in AD patients [35,36]. The minor (and probably clinically negligible) effects of these medications on cognitive decline and increased risk for neurological conditions, however, are the topics of a lot of debate [37].

Drugs for AD that are Currently Available:

The FDA has currently approved tacrine, galantamine, donepezil, and rivastigmine for use in treating AD. However, these cholinesterase inhibitors work differently and have specific undesirable side effects [38,39]. The primary monoaminoxidase-inhibiting reversible acetylcholinesterase inhibitor recognized by the FDA is tacrine (THA). The frontal and temporal areas of the brain's higher nicotine binding and increased glucose metabolism are associated with AD's cognitive impairments, which are mainly treated by tacrine [40]. As a result of various attempts to increase the selectivity of cholinesterase inhibitors, bifunctional THA was created; AChE's peripheral and catalytic regions are both where it binds. The drug's hepatotoxicity limits its use even though clinical trials indicated promise [41, 42]. Galantamine (GAL) is a reversible phenanthrene alkaloid that is more effective against AChE than BChE and is used to treat cognitive impairment. Additionally, GAL increases the synthesis of acetylcholine and other neurotransmitters by stimulating nicotinic receptors at various acetylcholine binding sites. Even though multiple studies have documented critical clinical trials, the situation is still unclear [43]. Donepezil is a piperidine derivative and reversible inhibitor that raises the concentration of acetylcholine for synapses to communicate. Donepezil has a long plasma half-life and is very selective. Numerous investigations revealed that donepezil was dose-related, had few side effects, and had the best tolerance [44]. Rivastigmine is a pseudo-irreversible inhibitor of butylcholinesterase and acetylcholinesterase from the carbamate complex with a brief plasma half-life. Rivastigmine is effective with reduced tolerability and exhibits selective activation in the cortex and hippocampus. Although rivastigmine therapy is clinically significant, it can only reduce the disease's course rather than halt it [45].

Heterocyclic compounds reviewed as anti-AD agents:

In medical chemistry and the pharmaceutical business, heterocyclic substances are essential. Cancer, AIDS, circulatory disorders, CNS disorders, and diabetes are among the illnesses that are regarded as the most significant risks to society. The fact that most heterocyclic derivatives are utilised as medications to treat these illnesses shows the need for new heterocyclic compounds.[46] Due to their extensive pharmacological activity, medicinal chemists have been interested in the bioactive heterocycles, which include oxygen, nitrogen, and sulphur and contain five and six-membered rings. The pharmacological properties of bioactive heterocyclic compounds can potentially treat several illnesses. As of now, the FDA has approved the use of donepezil, galantamine, and rivastigmine for the treatment of AD. The pharmacophoric characteristics of heterocyclic compounds are comparable to those of galantamine imitators. Therefore, the capacity of novel compounds containing these moieties to inhibit acetyl and butylcholinesterase should be tested. Nowadays, a wide variety of heterocyclic scaffolds have the potential to treat Alzheimer's. Because it uses ecologically friendly protocols and less dangerous chemicals, the faster and greener bioactive heterocycles synthesis has recently received much interest [47]. This review also covers the most critical research on the heterocyclic scaffold and its potential anti-Alzheimer

effects. It currently stands as the fifth leading cause of mortality among all conditions. The quest for pioneering medications in dementia care is imperative since there is currently no cure for this condition [48]. Stanciu et al., (2019) emphasise the established acknowledgement of Alzheimer's disease (AD) as the primary risk factor for dementia, notably within the framework of the cholinergic theory, the key factors contributing to AD include diminished acetylcholine production, accumulation of the enzyme acetylcholinesterase (AChE) responsible for acetylcholine breakdown, and the degeneration of neurons that produce acetylcholine. These are considered the primary causal elements in the development of AD. Additional factors contributing to Alzheimer's disease (AD) symptoms involve anomalies in the structure of cholinergic synapses, the elimination of specific acetylcholine receptor subtypes, and disruptions in cholinergic neurotransmission [49]. According to Lahiri et al., (2002), AChE (acetylcholinesterase) plays a role in the generation of amyloid (A) and a proteolytic fragment derived from APP (amyloid precursor protein), both significantly influencing the onset and progression of AD [50]. As per Greig et al., Acetylcholine acts as a neurotransmitter, aiding in the transmission of electrical impulses between nerve cells and enabling communication among them. AChE and butyrylcholinesterase are two distinct enzymes that play a significant role in the hydrolysis of cholinergic neurotransmitters. Cholinesterase is recognised as a potentially valuable target for Alzheimer's disease (AD) due to the vital role of both enzymes in regulating acetylcholine levels, making them significant targets for addressing cholinergic deficiencies [51]. According to Nguyen's 2022 publication, the four main acetylcholinesterase inhibitors that have received commercial approval are donepezil, tacrine, galantamine, and rivastigmine [52]; the identification of side effects, suboptimal drug pharmacodynamics and pharmacokinetics; lack of selectivity, and insufficient drug dosage as frequent causes for therapeutic failure was a collective observation. It is imperative in Alzheimer's disease (AD) therapy to discover more potent and efficient cholinesterase inhibitors by modifying the principal template structures of those currently available in the market. Recent research indicates that heterocyclic compounds have various biological effects, including those of antioxidants, anti-inflammatory drugs, enzyme inhibitors, etc. Amazingly, heterocyclic substances have been shown by Mughal et al., 2019 to block the AChE and butyrylcholinesterase enzymes [54]. According to Turkan et al., (2018), tacrine is the conventional treatment for AD. Nevertheless, pyrazole derivatives demonstrated even greater efficacy as butyrylcholinesterase inhibitors (Ki = 50.36–88.36 nM) and AChE (Ki = 44.66–78.34 nM) than tacrine. This underlines the necessity for exploring additional drug candidates containing heterocyclic structures in the pursuit of potential treatments for Alzheimer's disease.[55]. R. Sekioka et al., introduced new imidazopyridine analogues in 2020, building upon the structure-activity relationship (SAR) data derived from a lead compound 1 (Fig. 3), previously identified by the same research group. The A-B ring system, N-ethylpyridine-2-carboxamide of compound 1, exhibited metabolic stability. Additionally, a biphenyl moiety (D ring) was incorporated to bolster the compound's pharmacokinetic (PK) properties. Given the significant role of γ-Secretase in the production of the Ab peptide from the Ab protein precursor (APP), a process linked to the aetiology of Alzheimer's disease, investigations into γ-Secretase have been undertaken as a potential target for AD therapy. It could be conceivable to tweak c-secretase to prevent APP proteolysis in an incredibly hostile way to the Notch signalling system or to change how A proteins are produced so that they are converted into shorter, less harmful pathogenic peptides [56]. In in vitro examinations, both lead compounds 1 and 2 exhibited notably high levels of c-secretase modulatory activity. These compounds demonstrated substantial effectiveness in altering c-secretase activity within in vitro studies. Moreover, one of these compounds notably decreased the levels of Ab42 in mouse brains by 36%, all while avoiding in vitro CYP3A4 inhibition. As stated by M.S. Wolfe (2012, Compound 1 necessitated substantial

clinical enhancements in terms of effectiveness, displaying a 13% reduction in Ab42 levels in rat brains and exhibiting significant microsomal clearance (CLint in rat = 835 ml/min/kg). This research aimed to identify a potent multifunctional c-secretase modulator with neuroprotective attributes, addressing concerns related to metabolic stability and reducing Ab42 levels in plasma and the brain in rats.

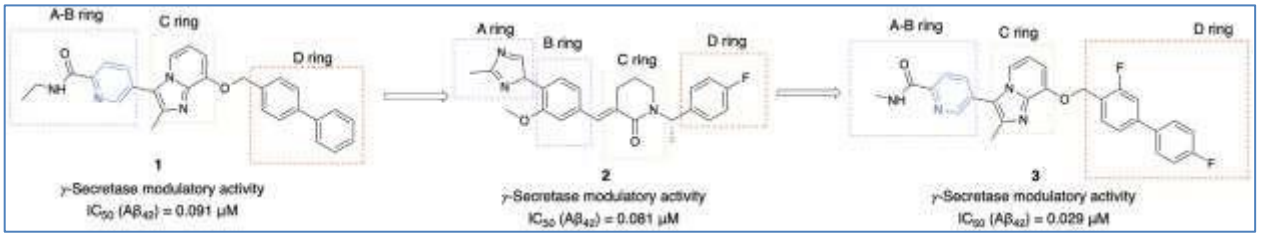

Fig.3 Novel imidazopyridine analogs

Pyrimidine, Pyridazine, and pyrazine all include the basic nucleus group diazine, and each one contains a benzene ring with two nitrogen atoms in place of the original two carbon atoms. M.S. Wolfe, in 2007, noted that all diazine rings are weaker bases than pyridine due to the inductive effect caused by the second nitrogen. These diazines showcase a diverse range of biological activities, spanning from anti-HIV, anti-inflammatory, antibacterial, antituberculosis, depressive, diuretic, anticonvulsant, and anticoagulant to anticancer properties [57]. In pursuing effective anti-neuro-inflammatory treatments for Alzheimer's disease, a fragment-based drug design (FBDD) approach was employed to construct a small library of piperazinyl-pyrimidine derivatives [58]. From compound 11 (GIBH-130, recognized as a potent anti-neuro-inflammatory drug), the piperazinyl-pyrimidine fragment (highlighted in red) and the stilbene moiety (marked in green) from resveratrol 12 were selected to form a composite structure (generic structure, GS-1 in Fig. 4), aimed at investigating anti-neuro-inflammatory activity. The discovery of compound 11 using microglia-based phenotypic screening and its powerful anti-inflammatory properties (IC50 = 3.4 nM) were first published by J. Easmon et al. in 2001. Furthermore, in Ab-induced and APP/PS1 double transgenic AD mice models, compound 11 exhibited a significant reversal of cognitive decline at a notably lower dosage of 0.25 mg/kg. [59].

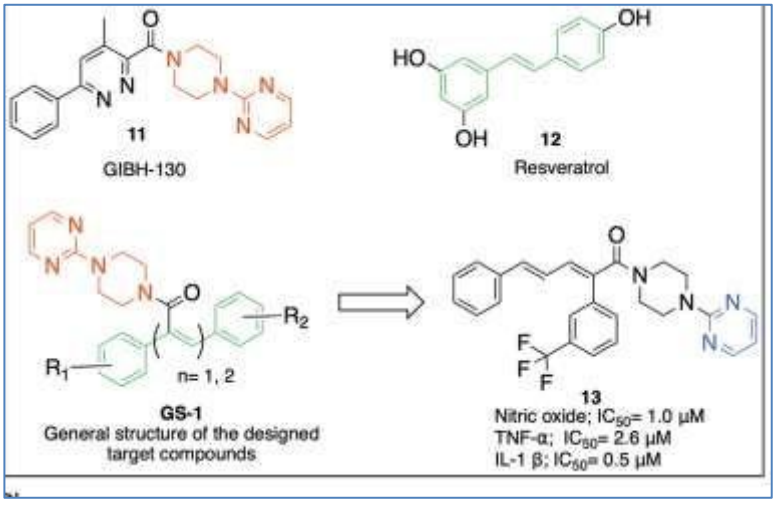

Fig.4 Piperazinyl-pyrimidine fragments

Heterocyclic compounds' role in preventing AD:

Currently, one of the significant health issues that primarily affects the elderly is Alzheimer's disease. Only five AD treatments have received FDA approval to date, and Tacrine is one of them that has been taken off the market due to its hepatotoxic effects. Except for the advancement of contemporary technologies to battle AD, the terrible pathology of AD disproportionately affects the elderly population, with estimates of its global prevalence ranging from 5 million in 2014 to 13.8 million in 2050 [60]. Researchers have studied the work of developing innovative chemicals that will be used to improve therapeutic medications with few adverse effects during the past many decades. The significance of five- and six-membered heterocyclic compounds has been the subject of several investigations [61]. Due to their valuable applications, heterocyclic molecules containing nitrogen, oxygen, and sulfur play a significant role in medicinal chemistry [62]. According to several studies, compounds with nitrogen heterocyclic compounds, such as triazoles, pyrazoles, and benzimidazoles, have antibacterial, anti-inflammatory, and anticancer activities [63]. Additionally, the oxygen and sulfur heterocyclic chemicals benzofuran, benzopyran, and pentathiophene have antioxidant, antibacterial, and anticancer effects.

CONCLUSION:

A deadly neurological illness that attacks the nerve cells in the brain is called Alzheimer's disease. There is currently no cure for this illness, while there are medications that can be used to reduce the disease's course. Researchers combine potent naturally occurring molecules with fewer adverse effects to offset the increased demand for medicines. Among them, heterocyclic compounds are crucial for their advantageous pharmacological effects. A large number of Phyto compounds that are utilized as medicines to treat a variety of illnesses also have a core of heterocyclic molecules. According to the findings of the multiple literature evaluations, heterocyclic compounds constitute a promising alternative to recently created cutting-edge neuro-protective AD treatments. Early administration of medications and tracking of patients for disease progression via biomarker diagnostics are also essential to the effectiveness of AD care. Future therapies that concentrate on the pathology of tau and combined treatment may slow the pathology's development in AD. To treat AD patients and those who are at risk of acquiring the illness, a powerful, clever, and successful medicine must be created.

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