BIOLOGICAL SIGNIFICANCE OF PROPARGYLAMINE DERIVATIVES: AN OVERVIEW

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Abstract: Propargylamine, due to its distinctive properties, holds significant prominence in medicinal chemistry and chemical biology. Its notable reactivity has long fostered the creation of propargylamine derivatives through diverse synthetic approaches. These strategies have notably eased accessibility to these compounds, enabling extensive exploration of their biomedical capabilities. This comprehensive review delves into and evaluates the diverse applications of propargylamine-derived compounds in drug discovery. It encompasses perspectives from both medicinal chemistry and chemical biology, identifying key therapeutic domains influenced by these compounds. Additionally, it discusses their current influence and burgeoning potential within these fields.

Keywords: Propargylamine, medicinal chemistry, chemical biology, drug discovery, organic chemistry

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1. Introduction: Propargylamine, a chemical component, holds significant prominence within medicinal chemistry and chemical biology due to its distinct properties. Its specific reactivity has traditionally led to the widespread creation of derivatives through diverse synthetic methods. These strategies have greatly simplified the production of propargylamine derivatives, enabling extensive exploration of their biomedical capabilities in research. [1-2] Propargylamines represent a highly versatile category of compounds that find wide-ranging applications. Among these, propargylamine derivatives including pargyline, rasagiline, and selegiline (Fig.1) exhibit utility in addressing neurodegenerative conditions such as Parkinson's and Alzheimer's diseases. Specifically, selegiline has been identified to possess antiapoptotic properties, rendering it valuable for both symptomatic relief and neuroprotective interventions. [3-5]

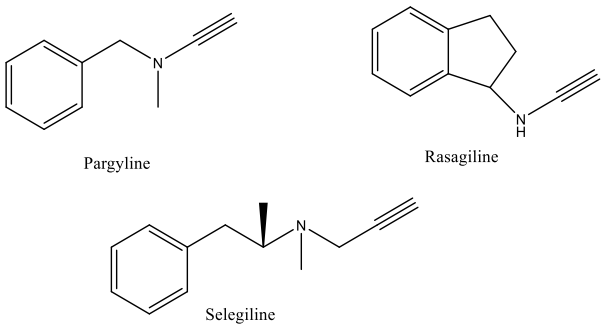


Fig. 1: Chemical structures of some highly important propargylamine-derivatives

Pargyline, chemically known as N-methyl-N-propargylbenzylamine, functions as a monoamine oxidase inhibitor. Within the two isoforms of monoamine oxidase (MAO), MAO-B specifically contributes to neurodegenerative conditions like Alzheimer's disease. Pargyline operates as a selective and irreversible inhibitor of MAO-B, serving as a pharmaceutical agent. [6-7] Beyond its role as an MAO inhibitor, pargyline finds application intreating type 1 diabetes and its associated cardiovascular complications. Additionally, it inhibits lysine-specific-demethylase-1 (LSD-1).

When combined with the chemotherapeutic agent camptothecin, pargyline demonstrated an augmented inhibition of LSD-1, leading to induced senescence and the inhibition of cancer cell growth. Furthermore, pargyline has shown inhibitory properties against proline-5-carboxylate reductase-1 (PYCR1), which renders it potentially beneficial in cancer treatments. [8-9] Rasagiline functions by inhibiting apoptosis through the reduction of oxidative stress, thereby stabilizing mitochondrial membranes. Additionally, it has shown promise in exhibiting neurorestorative properties. Clinical studies have established its effectiveness both as an independent treatment and when used alongside levodopa in managing Parkinson's disease. Furthermore, hybrid molecules derived from rasagiline have exhibited potential anti-Alzheimer's disease activities. [10-11]

This review emphasizes the significance of propargylamine derivatives in the field of medicine, showcasing a range of these derivatives along with their respective biological activities.

2. Biological Activity

2.1 Anti-Alzheimer disease activity:

Among neurodegenerative disorders, Alzheimer’s disease (AD) ranks as the fourth leading cause of mortality and stands as the predominant cause of dementia within the elderly demographic, impacting over seven million individuals globally.[12] The main clinical presentation involves a gradual decline in memory and shifts in brain function,

showcasing disrupted behaviour and difficulties in language and understanding. These symptoms worsen gradually over a period of 5 to 10 years. Much of these cognitive issues stem from the reduction of basal forebrain cholinergic neurons, causing a decline in cholinergic neurotransmission.[13]

Propargylamines are compounds featuring a propargyl component that commonly inhibits MAO-B, including well-known substances like selegiline (*l*-deprenyl), rasagiline, and PF9601N (Fig. 2). Selegiline was the initial selective MAO-BI used in Parkinson's disease treatment clinically. However, rasagiline (2) and PF9601N (4) represent a newer generation of MAO-BIs. Unlike selegiline (3), they do not produce amphetamine derivatives during metabolism.[14] Additionally, these compounds exhibit anti-apoptotic properties independently of their MAO-B inhibition capabilities.

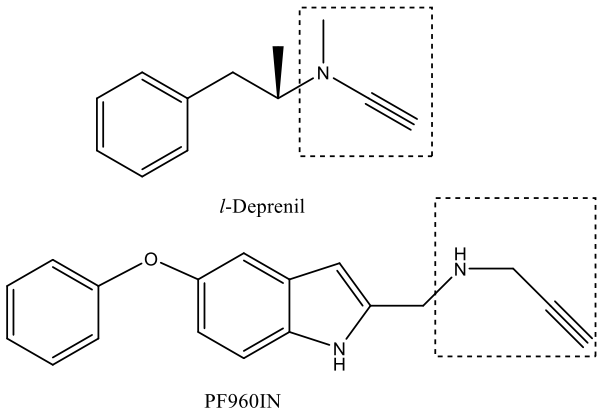


Fig 2. Chemical structures of some propargylamine-derived MAOI (propargylamine moiety is highlighted with dotted lines)

A series of tacrine–propargylamine derivatives were synthesised by *Mao et al* (2015) [15] and evaluated as possible anti-Alzheimer's disease (AD) agents (Fig 3). Presently, the FDA-approved most effective treatments for AD consist of four cholinesterase inhibitors (ChEIs): tacrine, donepezil, rivastigmine, and galantamine. Additionally, there's memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist sanctioned in 2003 specifically for moderate to severe AD treatment.[16]

They have provided synthesis and evaluation of a series of tacrine–propargylamine derivatives as anti-AD agents (Fig 4). *Guo et all* (2021) rationally designed twenty-nine hybrids of *N*-propargylamine-hydroxypyridinone which are the promising structures for the discovery of multitargeted ligands for AD therapy (Fig 5).[17] The hybrids exhibited encouraging iron-chelating and potent MAO-B inhibitory activity in the conducted in vitro tests. Specifically, the hybrid demonstrated promising iron chelation and effective MAO-B inhibitory activity in these experiments.[18]

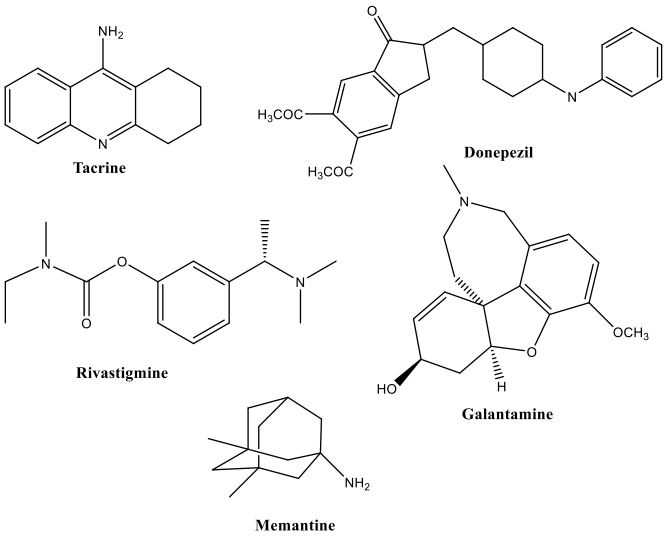


Fig 3. Chemical structure of Tacrine, Donepezil, Rivastigmine, Galantamine and Memantine

Seven **DPH** Hybrides were synthesized by reaction of **D**onepezil, **P**ropargylamine and 8-**H**ydroxyquinoline for the potential prevention and treatment of Alzheimer's disease by Wang et al. (Fig. 6). [19]

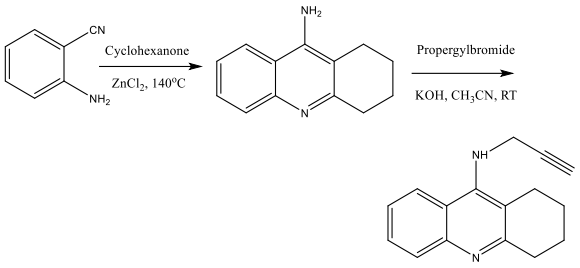


Fig 4. Synthesis of tacrine–propargylamine derivatives

In addressing AD, targeting monoamine oxidase (MAO) is crucial. This enzyme facilitates the breakdown of various natural and foreign amines, generating Hydrogen peroxide as a significant intermediary through the Fenton reaction. This process leads to the creation of harmful oxygenated radicals, which play a role in the advancement of AD.

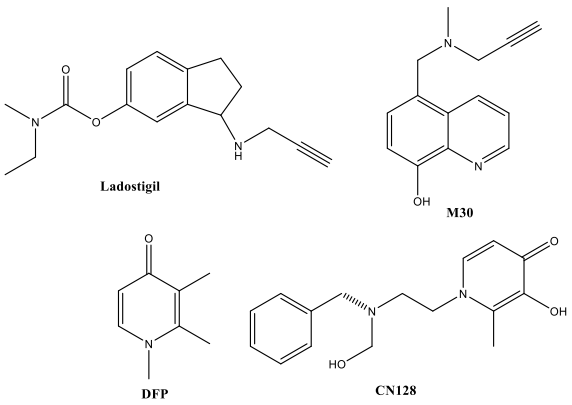


Fig 5. Structures of representative *N*-propargylamine and hydroxypyridinone derivatives

In adherence to the MTDL drug design strategy, *Youdim and colleagues* conceived and crafted Ladostigil (Fig. 5) by integrating the carbamate ChE inhibitory segment from the anti-Alzheimer's drug, rivastigmine (Fig. 7), into the 6th position of the MAOI rasagiline.[20]

This resultant compound functions as a dual inhibitor for both AChE and BuChE. Its inhibitory efficacy is approximately 100 times more potent against AChE than BuChE.

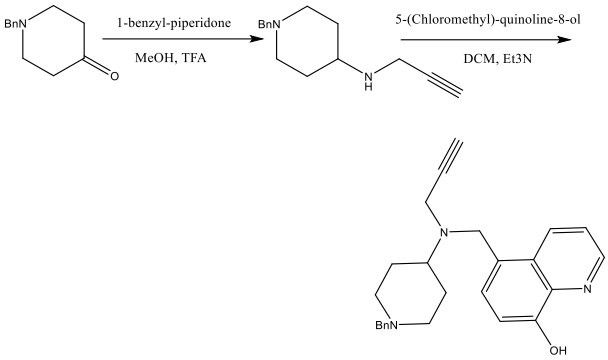


Fig. 6 Synthesis of DPH

Moreover, ladostigil serves as a brain-selective inhibitor for both MAO A and MAO B, exhibiting minimal to no peripheral MAO inhibitory effects. This crucial attribute allows compound crafted ladostigil to induce only limited potentiation of blood pressure in response to oral tyramine (Fig. 7), underscoring its significance.

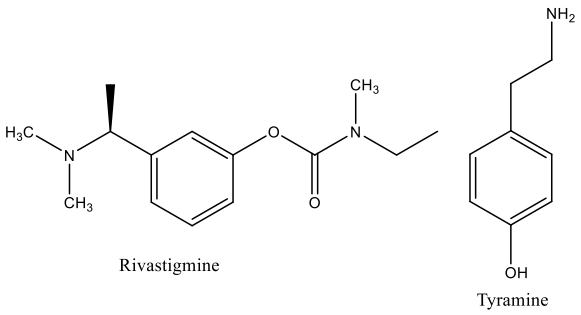


Fig 7. Current AD pharmacotherapy drugs

2.2 Anti Perkinson disease Activity:

Rasagiline (N-propargyl-(1R)-aminoindan), an anti-Parkinson drug, fosters neuronal survival through its neuroprotective activity associated with the propargyl moiety (propargylamine).[21] Rasagiline, an anti-Parkinson drug and highly potent selective irreversible inhibitor of monoamine oxidase (MAO)-B, demonstrates

neuroprotective and antiapoptotic effects in both cell cultures and in vivo.[22]

Rasagiline, identified as N-propargyl-(1R)-aminoindan, is a highly potent and selective irreversible inhibitor of monoamine oxidase (MAO)-B. It has demonstrated neuroprotective and antiapoptotic effects against various insults in both cell cultures and in vivo, successfully completing phase III clinical trials for Parkinson's disease. In a current study, *Youdim et al* illustrate that rasagiline at concentrations of 1 and 10 μM significantly shields rat PC12 cells from β-amyloid (Aβ1-42) toxicity.[23] Moreover, rasagiline markedly enhances the secretion of the nonamyloidogenic soluble form of the amyloid precursor protein (sAPPα) by approximately threefold in SH-SY5Y neuroblastoma and PC12 cells.

Rasagiline, a potent second-generation monoamine oxidase (MAO) B inhibitor used in Parkinson's disease treatment, has been the subject of a review by *Youdim et al in* 2005. This review sheds light on the molecular mechanism of neuroprotection facilitated by rasagiline and its derivatives, particularly the N-propargylamine moiety. The neuroprotection extends to shielding against various neurotoxins that trigger the opening of the mitochondrial permeability transition pore (MPTp). This process involves the Bcl-2 protein family, associated with protein kinase C (PKC) pathway activation, and interaction with mitochondrial permeability transition (MPT). These intricate processes play pivotal roles in neuronal survival and the functions of neuronal trophic factors.[24]

2.3 Antioxidant activity:

In the quest for innovative, low-toxic, cell-penetrating, and neuroprotective antioxidants, A. Kochman and collaborators have formulated several novel N-propargylamine derivatives of nitroxyl, labelled as "JSAKs." [25] The reactivity and antioxidative efficacy of two chosen JSAKs, along with their parent nitroxyl, were assessed in vitro using cell-free γ-radiolysis and model Fenton-type reaction systems. These findings were then compared with the reactivity of deprenyl, a investigated member of adjunct therapies in clinical neurology. Additionally, the ability of JSAKs to inhibit the oxidative degradation of a model target(deoxyribose), deprenyl, and dopamine induced by hydroxyl radical (OH) was explored (Fig 8).

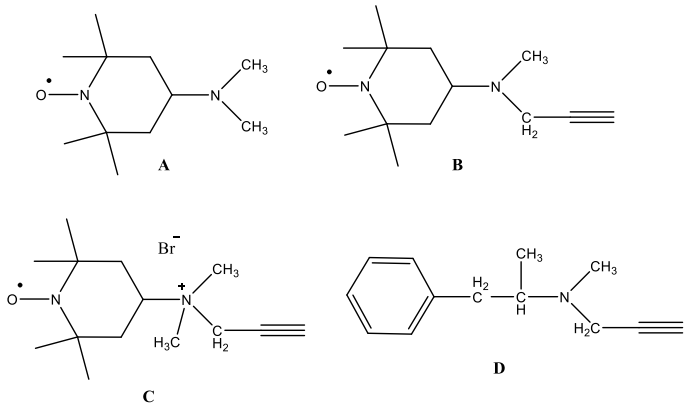


Fig 8. Novel N-propargylamine derivatives of nitroxyl labeled as "JSAKs

They further added that the identified antioxidant and protective capabilities of the recently developed N-propargylamine nitroxyls, known as JSAKs, either independently or in conjunction with deprenyl (DEP), could substantiate the contemporary "concept of neuroprotective treatment strategies." Conducting thorough investigations into their in vitro and in vivo activities may lead to the development of versatile antiparkinsonian agents with therapeutic applications in Parkinson's disease (PD). In PD, the targeted generation of cytotoxic reactive oxygen species (ROS) in the basal ganglia stands out as a crucial neurotoxic mechanism contributing to nigrostriatal degeneration and apoptotic neuronal death. A range of aryl propargylamines, featuring diverse substitutions in the hydrogen at the p-position and within the propargyl moiety, were investigated for their potential as peroxynitrite scavengers by *Dragony et al*. [26] The assessment of their scavenging activity involved the peroxynitrite (ONOOÿ)-mediated

oxidation of dichlorofluorescin and linoleic acid, measured through dichlorofluorescein formation and oxygen consumption, respectively.

Among the compounds examined, only 1-phenylpropargylamine (AP3) exhibited concentration-dependent inhibition of ONOOÿ-induced dichlorofluorescin and linoleic acid oxidation, with IC50 values of 637 and 63 M, respectively. Spectral changes in UV-visible absorbance properties of AP3 in the presence of peroxynitrite indicated the formation of a novel compound, later identified as phenylpropargyl alcohol through gas chromatograph–mass spectrometer analysis. Structure–activity relationship analysis suggested that the scavenging activity of AP3 was attributed to the aminopropargyl moiety and the availability of the nitrogen electron pair (Fig 9).

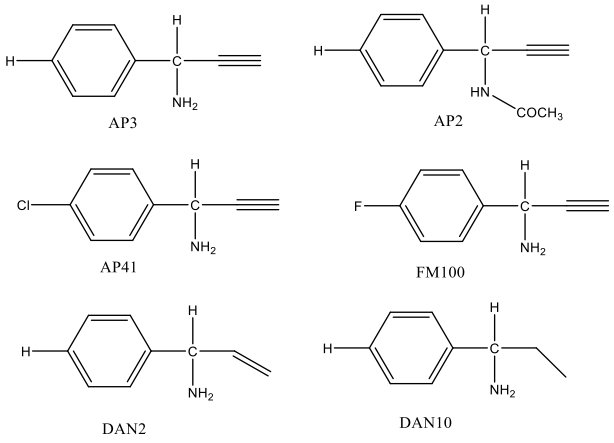


Fig 9: Chemical structure of synthesized propargylamines

2.4 Cytotoxic Activity:

While toxicity is a broad term referring to the overall harmfulness of a substance to an organism, cytotoxicity specifically addresses how toxic a substance is to cells. A cytotoxic compound has the potential to induce cell damage or death, through processes like necrosis or apoptosis. The extent of cytotoxicity varies among different substances, and researchers seek to quantify the cytotoxic levels of a chemical to ensure it is not detrimental or fatal to patients. Examples of cytotoxic agents encompass chemotherapy drugs and specific venoms.[27]

Twenty-six analogues of propargylamine mycophenolate were formulated and synthesized from mycophenolic acid (Fig 10), employing a pivotal A3-coupling reaction. Their cytotoxicity was assessed across six cancer cell lines. These compounds demonstrated selective cytotoxic effects on neuroblastoma (SH-SY5Y) cancer cells, displaying lower toxicity towards normal cells compared to the reference compound MPA 1 and the standard drug ellipticine. The propargylamine mycophenolate scaffold emerges as a promising foundation for the advancement of novel anticancer drugs targeting neuroblastoma. [28]

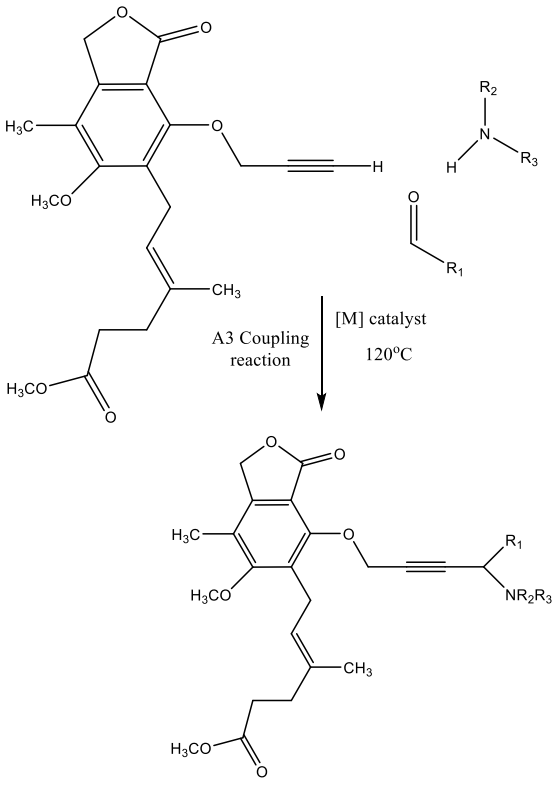
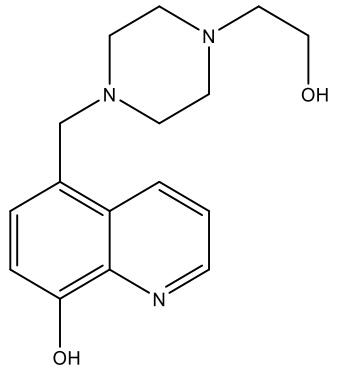


Fig 10. A3-coupling reaction for the synthesis of propargylamine mycophenolate.

2.5 Neuroprotective Agent:

Weinreb and colleagues spearheaded the development of M30 (Fig 5), a multi-faceted neuroprotective compound. M30 was engineered by combining the propargyl moiety from rasagiline (Fig. 11) with the 8-hydroxyquinoline derivative of VK-28, an antioxidant iron chelator. Behavioural evaluations demonstrated that M30 mitigated cognitive deficiencies across various spatial learning tasks, memory retention, working memory, learning capacity, anxiety levels, and memory related to new food and nesting behaviour in mice. Given M30's targeting of specific pharmacological sites linked to AD, it shows promise as a potential drug for neuroprotection and restoration in treating the disease. [29]



VK 28

Fig. 11: Chemical structure of VK 28

Several drugs have been suggested as potential candidates for neuroprotective trials. Notably, rasagiline (N-propargyl-(1R)-aminoindan), recognized as a potent, selective, and irreversible inhibitor of monoamine oxidase (MAO)-B, commonly used as an anti-Parkinsonian medication, and other compounds like propargylamines, demonstrate neuroprotective properties.

Recent clinical trials involving Parkinsonian patients revealed that individuals receiving rasagiline treatment for 12 months experienced notably less functional decline compared to those whose treatment initiation was delayed by 6 months. This observation hints at the potential disease-modifying effects of rasagiline, possibly aligned with findings from cell culture and animal studies highlighting its neuroprotective properties. Moreover, recent research has demonstrated that free propargylamine, akin to rasagiline, demonstrates neuroprotective effects against apoptosis triggered by serum deprivation and the endogenous neurotoxin N-methyl(R)salsolinol. [30]

Frank et al reported on twelve novel polycyclicamine cage derivatives, synthesized with or without a propargylamine function, designed to possess inherent multifunctional neuroprotective activity. Rasagiline and selegiline are second generation propargylamine derivatives that irreversibly inhibit brain MAO-B, and have promising neuroprotective activities.
Synthesis and evaluation of pentacycloundecane and hexacycloundecane propargylamine derivatives as multifunctional neuroprotective agents (Fig. 12). [31]
Their effectiveness stems from the propargyl component, which, upon oxidation, interacts with the flavin prosthetic group situated within the active site of the MAO-B enzyme. This interaction leads to the formation of a covalent adduct at the N5 position of flavin adenine dinucleotide (FAD). Additionally, the propargyl component is recognized for its significant role in offering neuronal and mitochondrial protection, along with anti-apoptotic characteristics. This particular component has proven especially valuable for integrating into multi-functional compounds with inherent MAO-B inhibitory capabilities. [32]

2.6 Neurorescue activity:

The neuroprotective properties of rasagiline (N-propargyl-(1R)-aminoindan), an anti-Parkinson drug, are attributed to its propargyl moiety (propargylamine), which promotes neuronal survival. Bar-Am and colleagues explored the neurorescue effects of propargylamine in a model of progressive neuronal death induced by prolonged serum deprivation in human SH-SY5Y neuroblastoma cells. [33]

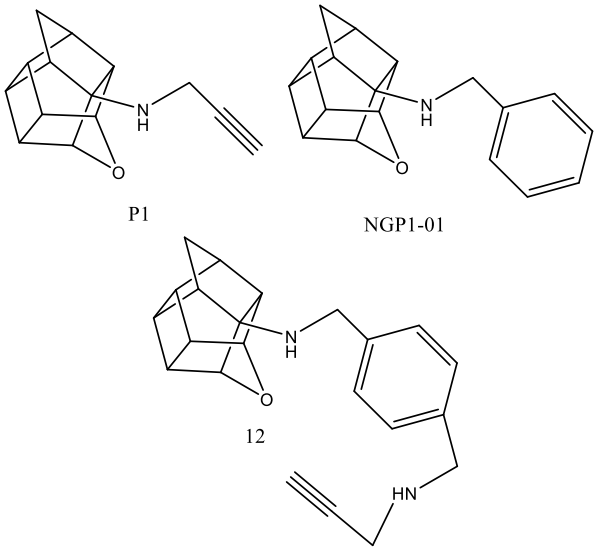


Fig 12. Neuroprotective drugs

Propargylamine (0.1–10 μM) demonstrated a dose-dependent reduction in levels of the early apoptosis-associated phosphorylated protein, H2A-X (ser 139), and attenuated the cleavage of caspase-3 along with its substrate poly-ADP ribose polymerase (PARP). Furthermore, the compound significantly reversed the apoptotic effects caused by long-term serum withdrawal, including the down-regulation of the antiapoptotic protein, Bcl-2, and the up-regulation of proapoptotic proteins such as Bax, Bad, and Bim.

2.7 Monoamine oxidase inhibitor:

Monoamine oxidase (MAO, EC 1.4.3.4) facilitates the oxidation of monoamine neurotransmitters, neuromodulators, and exogenous bioactive monoamines. There are two forms of MAO, specifically MAO-A and MAO-B, with distinct distributions in neuronal and nonneuronal structures. [34]

Several N-substituted propargylamines are recognized by *Yu et al* as mechanism-based inhibitors of MAO. Clorgyline and deprenyl, in particular, serve as prototypical inhibitors for MAO-A and MAO-B, respectively. [35] In this current investigation, various ring-substituted deprenyl structural analogs were synthesized, revealing changes in selectivity and potency towards MAO-A and MAO-B activities. Notably, when deprenyl and its structural analogs underwent further modification to become their corresponding quaternary ammonium salts (Fig.13) by introducing an additional propargyl or a methyl group to the nitrogen atom— the inhibition potency against MAO-B activity was significantly diminished, while inhibition of MAO-A activity substantially increased.

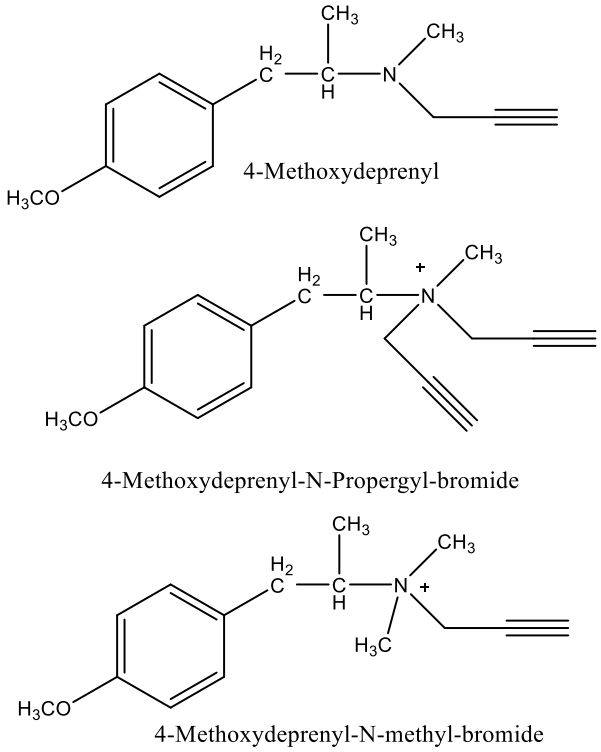


Fig 13. The chemical structures of the 4-methoxydeprenyl and its N-propargyl and N-methyl quaternary ammonium salts.

The initial exploration of multipotent MAO/ChE inhibitors involved the integration of a tricyclic indole carbamate segment from

the AChEI physostigmine with the characteristic propargylamine group found in MAOIs, as outlined by *Fink et al.* in 1996. This combination yielded compounds exhibiting effective dual inhibitory activities. Notably, Compound 9 (depicted in Fig. 5) demonstrated a particularly intriguing profile, featuring reversible behaviour towards MAO-A and thereby avoiding the undesirable side effects associated with irreversible inhibitors. Despite discontinuation of this approach due to identified limitations in oral activity and inadequate brain penetration, the findings established a foundational structural framework for the subsequent advancement of combined MAO/ChE inhibitors. [36]

From the extensive array of scrutinized derivatives, compound (depicted in Fig. 14) emerges with a highly compelling and promising profile, demonstrating potent inhibition of both MAOA and MAO-B. [37]

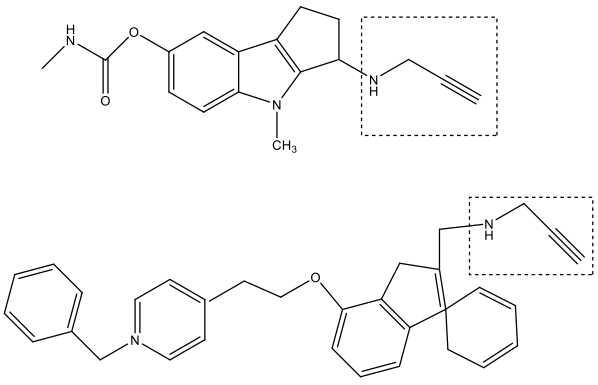


Fig 14. Structure of multitarget directed ligands having propargyl moiety

Chemical structures of propargylamine-containing multitarget-directed ligands (MTDLs) with dual MAO/ChE inhibitory activity was proposed.

3. Conclusion:

The existing body of literature highlights the versatility of the Propergyl moiety, suggesting its potential applications in drug discovery and medicine. This substrate exhibits diverse biological activities, making it promising for the development of novel and more effective chemotherapeutic agents. The future holds significant potential for the exploration of substituted benzimidazoles as a new class of compounds with improved efficacy, paving the way for advancements in the field.

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