WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 18, 316-332. Review Article ISSN 2277– 7105

PROPARGYLAMINE MOIETY: A VERSATILE SCAFFOLD FOR DRUG DESIGN AND DISCOVERY

Ankireddy Aswani[1]*, Bommana Pavani[2], Vardu Sravani[3] and Yerva Jahnavi Reddy[4]

[1]Osmania University, Department of Pharmaceutical Chemistry, Hyderabad, India.

[2]National Institute of Pharmaceutical Education and Research, Department of Pharmacoinformatics, S.A.S Nagar, India.

[3]Sri Krishnadevaraya University, Department of Pharmaceutical Sciences, Anantapuram, India.

[4]New Jersy Institute of Technology, Department of Bioinformatics, New Jersy, USA.

Article Received on
26 August 2023,

Revised on 16 Sept. 2023,
Accepted on 06 Oct. 2023

DOI: 10. 20959/wjpr202318-29918

***Corresponding Author**
Ankireddy Aswani
Osmania University,
Department of
Pharmaceutical Chemistry,
Hyderabad, India.

ABSTRACT

The propargylamine moiety gained a lot of attention in the fields of medicinal chemistry and pharmaceuticals due to its wide range of applications stemming from its chemical reactivity and structural advantages. For many years scientists strategically designed, synthesized and evaluated propargylamine derivatives for various pharmacological activities. They have also developed strategies to understand the mechanism, activity, structure activity relationship of propargylamine moiety broadly. From the extensive research it is evident that the propargylamine derivatives exhibit diverse array of pharmacological properties including anti-cancer, anti-apoptotic, Mono Amino Oxidase-B (MAO-B) inhibitory activity, anti-microbial, antioxidant, and many more which make them potential candidates in the drug design. This versatility of propargylamine moiety makes it an incredible multi-target ligand for many diseases. This review provides an overview of reported compounds with propargylamine moiety, and their pharmacological actions as described in the literature. With more research propargylamine derivatives can find their place in potential drugs treating common ailments to life threatening conditions in the future.

BACKGROUND

Medicine is ever-changing. There is always a need for more efficient and therapeutically safe drugs. The scientific community has been investing a lot in the research of new drugs. Compounds with propargyl amine moiety are one of those potential candidates which caught the attention of scientists for their promising bioactivities and remarkable structural advantages. The first piece of literature that reported the use of propargylamine dates to the 1940s to 1950s.[1] Chemically propargylamines are organic compounds with amine and an alkyne group. The alkyne group is electrophilic while the amine moiety is nucleophilic. This combination of alkyne and amine moiety in the same molecule allows these compounds to undergo various chemical reactions and provides endless possibilities for building pharmacophores that can be potential drug candidates.[2] Propargyl amine serves as a key precursor for the synthesis of pyrroles, pyrrolines, pyrrolidine, pyrazines, pyrazoles, thiazoles, thiazolidines, isoxazoles, oxazolidines, pyridines, dihydropyridines,[3] indolizines, oxazoles, quinolones.[4] It also acts as an essential element in the synthesis of isosteres, allylamines, β-lactams, conformationally restricted peptides, and oxotremorine analogs.[4] Propargylamine moiety is widely known for its neuronal, mitochondrial protective activities and anti-apoptotic properties. Propargylamine derivatives such as rasagiline and selegiline are widely accepted therapy for neurodegenerative disorders like AD and PD.[5] It is revealed that the ability of propargylamine moiety to inhibit MAO- B, suppress MpTp opening, the ability to regulate protein kinase C signaling, and Bcl-2 family proteins are also responsible for its neuroprotective action.[6] This diversity in the functionality of propargylamine moiety can make it a multi-target ligand to combat various neurodegenerative diseases.[7] Other propargylamine derivatives like paragyline is widely used as an anti-hypertensive agent while clorgiline with MAO-A inhibitory activity found its application as an antidepressant.[2]

There was more emphasis on the neuroprotective action of propargyl amine moiety at first but from the past few years in the search for multi-target drugs researchers successfully designed and synthesized various propargyl amine derivatives and studied different pharmacological activities and mechanisms of the compound in exerting that pharmacological activity. This approach extended their applications in modern medicine. In due course, propargylamines also found to possess cardioprotective[8], anticancer activity[9], and anti-microbial activity.[10] In some cases, this versatility of propargylamine moiety provides an added advantage of administering in combination with other drugs to reduce their side effects without interfering with their main therapeutic activity.

This review focuses on the research done on pharmacological activities and mechanism of action of propargylamine derivatives so far and highlights the highest activity-producing compounds reported in the literature. This review serves as a comprehensive study of MAO-B inhibitory activity, anti-apoptotic, anti-microbial, anti-cancer, anti-oxidant, peroxynitrite scavenging activity, cardioprotective activity, neuro-protective activity of propargylamine derivatives.

MAIN TEXT

Neuroprotective activity

Martin *et al. 2021*. developed a series of multi-target-directed ligands (MTDLs) by combining salicylic and cinnamic scaffolds and incorporating propargylamine substitutions. The synthesized compound's inhibitory effect on the AChE and BuChE enzymes was evaluated using Ellman's method. The kynuramine technique was also used to evaluate the inhibition of MAO-A and MAO-B in invitro. The 5-Bromo-N-(prop-2-yn-1-yl) salicylamide (1e) was the most effective designed molecule at inhibiting AChE, whereas carbamates 2e and 2d significantly inhibited BuChE. 2D structures of 1e, 2d, 2e were mentioned in the Figure 1a, b, c respectively. The compound that had the lowest IC50 value was 5-bromosalicylidene Schiff base 4a, which showed strong MAO-A inhibition as well as proportional inhibition of AChE and BuChE, confirming its classification as a genuine MTDL. Additionally, the reactive oxygen species (ROS) levels caused by organic peroxide were significantly reduced by these substances (1e, 2d, 2e, and 4a), demonstrating their antioxidant capabilities. Due to their inhibitory efficacy against a variety of targets, including AChE, BuChE, MAO-A, and antioxidant effects, the findings imply that these compounds have assured as MTDLs. To investigate their therapeutic potential in the treatment of neurological diseases, further research and development are required.[11]

Samadi *et al.* 2012. conducted a synthesis of heterocyclic substituted alkyl and cycloalkyl propargyl amines, followed by pharmacological evaluation and molecular modeling studies. The aim of their studies was to design multipotent inhibitors that could thwart both cholinesterase (AChE/BuChE) and MAO-A/B enzymes simultaneously. Researchers discovered that compound 7 has significant MAO-B inhibitory action (IC50 = 31 ± 2 nM) and moderate selectivity for equine BuChE inhibition (IC50 = 4.7 ± 0.2 mM) via their assessments. Compound 12 on the other hand, which is directed towards the periphery anionic site, exhibited selective inhibition of AChE activity. These results led to the

identification of compounds 7 and 12(Figure 1d, 1e respectively) as lead molecules for the discovery of novel and promising medicines for the treatment of AD.[12]

Zindo *et al.* 2019. conducted a successful synthesis and evaluation of 12 propargylamine derivatives based on pentacycloundecane and hexacycloundecane structures, aiming to develop multifunctional neuroprotective agents. The compounds were assessed for their neuroprotective activities and potential to target multiple mechanisms. The study revealed that compounds **5** and **12**, both containing the propargyl moiety, exhibited the highest overall activity as effective multifunctional neuroprotective agents. These compounds demonstrated inherent calcium regulatory potential by blocking voltage-gated calcium channels (VGCC) and N-methyl-D-aspartate receptors (NMDAr), while also displaying inhibitory capacity against MAO-B. Based on these findings, compounds 5 and 12 showed promise as neuroprotective agents with the ability to target multiple pathways. Their multifunctional properties make them potentially valuable in the treatment and prevention of neurological disorders.[13]

Xu *et al.* 2018 developed a novel series of propargylamine-modified 4-aminoalkyl imidazole substituted pyrimidinylthiourea derivatives as MTDLs by incorporating the propargylamine pharmacophore into the pyrimidinylthiourea scaffold. The activities of the produced compounds against the enzymes AChE, BuChE, MAO-A/B, and antioxidant capacity were assessed. They found via biological experiments that compound 1b had effective selective inhibitory actions against AChE (IC50 = 0.324 μM, selectivity index > 123) and MAO-B (IC50 = 1.427 μM, selectivity index > 35). Additionally, they deduced from SAR investigations that the degree of the propargylamine moiety's nitrogen atom substitution had a significant impact on the inhibition of AChE and MAOs. As a result of its specific inhibitory actions against AChE and MAO-B, compound **1b** whose 2D structure was mentioned in **Figure 1f**, may hold promise as a possible therapeutic drug, according to the findings. Further research must be done to determine the beneficial effects of these MTDLs modified with propargylamine pyrimidinylthiourea derivatives.[14]

***Mao et al.* 2015.** synthesized tacrine-propargylamine compounds and their effectiveness as acetylcholinesterase (AChE) inhibitors was evaluated. Their study's findings suggested that compounds 3a and 3b had superior activity and showed a good balance between inhibiting AChE and butyrylcholinesterase (BuChE). Concerning inhibiting AChE and BuChE specifically, compound 3a showed IC50 values of 51.3 nM and 77.6 nM, respectively.

Similar to compound 3a, compound 3b displayed IC50 values for the inhibition of AChE and BuChE of 11.2 nM and 83.5 nM, respectively. When compared to tacrine, an approved drug used to treat AD, these compounds showed higher levels of activity. As a result, substances 3a and 3b are regarded as promising lead molecules for the creation of possible therapies for AD. The 2D structure of 3a was mentioned the Figure 1g.[15]

To design multifunctional neuroprotective agents, **Zindo *et al.* 2014** created several polycyclic propargylamine and acetylene derivatives. The inhibitory action of these produced compounds against NMDA receptors, VGCC, MAO-B, and apoptotic processes was assessed. According to the findings, compounds **10, 12, 15, and 16** had the most inhibitory effects on VGCC, NMDA receptors, and apoptosis. Only substance 10 showed an inhibitory effect against MAO-B, though. The polycyclic propargylamines and acetylene derivatives have shown potential as new multifunctional neuroprotective drugs in light of these findings. The extent of their therapeutic.[16]

Sheunopa *et al.*2020 synthesized seven molecules in two series, adding a benzyloxy (series A) or diethyl carbamate (series B) moiety was attached to position 7 of the scaffold by an SN2 substitution followed by the α-bromination at position 3. Enzymatic studies were carried out against the MAO and cholinesterase enzymes, in vitro assay was performed to screen the compounds for their neuroprotective activity. Five compounds were more potent than rasagiline, with IC_{50} values between 0.497 µM and 0.029 µM. Finally, benzyloxy moiety (series A) imparts potent activity for MAOB selectivity and neuroprotection. Among all the synthesized compounds, SM3B and SM4A showed excellent activity for the treatment of AD whose 2D structure was mentioned the Figure 1h, 1i.[17]

Bhupinder *et al.* 2018 synthesized twenty novel 2,4,6-trisubstituted pyrimidine derivatives and screened them for their ability to inhibit MAO by using Amplex red assay. At quantities below micromolar, it was discovered that every chemical that was synthesized was reversible and selectively inhibited the MAO-B isoform. The most effective MAO-B inhibitor was MVB3, which had an IC_{50} value of 0.38:0.02 mm. In contrast, MVB6 and MVB16 were the most selective for MAO-B, with IC50 values of 0.51:0.04 mm and 0.48:0.06, respectively.[18]

To create powerful, focused, and reversible MAO-B inhibitors for the treatment of PD, propargyl-substituted pyrimidine derivatives might be potential leads. Among all the

synthesized compounds, MVB3 showed potent activity, the 2D structure was mentioned in Figure 1j.

In dopaminergic neuroblastoma SH-SY5Y cells, **Maruyama *et al.* 2003** investigated the neuroprotective effects of TV3326, TV3279, and related compounds for their potential protection against apoptosis and the decline in mitochondrial membrane potential (DCm) related to apoptosis induced by the peroxynitrite-generating agent, SIN-1 [N-morpholinosydnonimine]. According to the researchers, TV3326 and rasagiline were the most effective in reducing the apoptosis that was triggered by 250 mM SIN-1. The study also revealed that the anti-apoptotic properties are due to the propargyl moiety. They also suggested that the compounds may also be potential neuroprotective therapy for not only AD but also for Lewy Body disease, an extrapyramidal disorder associated with dementia.[19]

Yogev -Falach *et al*. 2003 in their study showed the rasagiline (1 and 10 µM) protective action against β-amyloid (Aβ1-42) toxicity in rat PC12 cells. The study also showed that rasagiline greatly boosted (by roughly a factor of three) the production of the soluble form of the amyloid precursor protein (sAPP) from PC12 and SH-SY5Y neuroblastoma cells. Ro31-9790 (100 µM), a hydroxamic acid-based metalloprotease inhibitor, inhibited the rise in sAPP in a dose-dependent manner, indicating that the impact is mediated by α-secretase activity. The study demonstrated that rasagiline, TVP1022, and propargylamine (that lacks cholinergic activity) stimulated sAPPα release and MAPK phosphorylation which was recently found for TV3326 (Non-MAO inhibitor) also. Rasagiline's activities were contrasted with those of its S-isomer, TVP1022, proving that MAO-B inhibition is not necessary for either rasagiline's neuroprotective effects against Aβtoxicity or the sAPP-α induced release and activation of MAPK. The research contributed to clarifying how important a function the propargyl moiety plays in these compounds.[20]

Mezeiova *et al*.2021 designed ten novel derivatives of 2-propargylamino-naphthoquinone. These substances have been examined biologically for their ability to inhibit MAO A/B, prevent beta-amyloid aggregation, scavenge free radicals, and chelate metals. The study determined the BBB permeation ability of these compounds using a Parallel artificial membrane permeability assay (PAMPA). On human neuroblastoma (SH-SY5Y) and murine microglial (SIM-A9) cell lines, the cytotoxic profiles were assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) test using Rasagiline as a reference. The most cytotoxic of all the studied compounds were 14 and 15, whereas

compound 18 had more potent radical scavenging abilities than clioquinol in the presence of Cu (II) ions. While compound 14 displayed strong MAO inhibition and metal-chelating capabilities, it demonstrated adequate inhibitory efficacy against Aβ aggregation. 2D structures of compounds 14, and 18 are mentioned in **Figure 1k, 1l.**[21]

Nag *et al*. 2012 synthesized and assessed three new propargylamine compounds that were fluorine-18 labeled as possible PET radioligands to detect MAO-B activity. For this study, the two selected compounds were used in autoradiography tests on human postmortem brain tissue segments. Only compound 18 showed a strong preference for MAO-B over MAO-A, and it was chosen for further PET testing in a cynomolgus monkey. Compound **18 (Figure 1m)** can be regarded as a candidate for future PET research in humans because the study found that it is a selective MAO-B inhibitor in vitro and that it showed an MAO-B-specific binding pattern in vivo in monkeys.[22]

Yu *et al*.1992 synthesized a series of aliphatic propargylamine derivatives and examined them for MAO inhibitory activity in Rat liver mitochondria (in vitro) and Mouse brain (in vivo). The study found a correlation between chain length and the replacement of hydrogen on the terminal carbon of the aliphatic chain and the inhibitors' efficacy. The length of the aliphatic carbon chain increased with MAO inhibitory efficacy as measured in vitro. The inhibitory effect was significantly decreased by replacing the hydrogen atom on the nitrogen atom with an ethyl group, a hydroxyl, carboxyl, or carbethoxyl group at the aliphatic chain terminal, or both. The R-(-)-enantiomer was 20 times more active than the S- (+)-enantiomer and stereospecific effects were seen. When it comes to reducing brain MAO-B activity in vivo, shorter carbon chain lengths—four to six carbons—were shown to be more effective than longer chains, especially when administered orally. In the mouse brain, chronic low-dose treatment of the aliphatic propargylamine resulted in a minor cumulative suppression of MAO-A activity. According to the study's findings, these aliphatic propargylamines might be employed to treat several neuropsychiatric illnesses.[23]

Baranyi *et al.* 2016 described the effects of a new class of (hetero) aryl alkenyl propargylamine compounds with robust and specific MAO-B inhibitory activities that are protective against the supra-additive impact of mitochondrial dysfunction and oxidative stress. These drugs were evaluated in vivo utilizing 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) produced acute, sub chronic, and chronic experimental models of PD in mice as well as in vitro on acute rat striatal slices pretreated with the complex I

inhibitor rotenone. In the rat striatum, the chemicals consistently inhibited pathological dopamine release caused by oxidative stress in vitro as well as the production of toxic dopamine quinone. They also restored tyrosine hydroxylase-positive neurons in the substantia nigra following rotenone therapy. Using acute and sub chronic, delayed application procedures, the compounds also demonstrated notable protective benefits against in vivo MPTP-induced striatal dopamine depletion and motor impairment in mice. In a chronic mouse model of MPTP plus probenecid (MPTPp) treatment, which causes a gradual loss of nigrostriatal dopaminergic neurons, one chemical, SZV-558 (**Figure 1n**), was also looked at and found to be protective. The study's findings suggested that these chemicals would work well as PD treatments.[24]

Jianan *et al*.2021 reported a series of N-propargylamine-hydroxypyridinone analogs that shows greater iron-chelating potential (pFe^{3+}=17.09-22.02) and robust MAO B inhibitory effect. All these positive outcomes demonstrated the viability of the N-propargylamine-hydroxy pyridinone scaffold as a platform for the identification of multi-targeted ligands for the treatment of AD. Among all the compounds, **6b (Figure 1o)** was found to be potent and underwent a series of biological assessments, including mice behavioral testing, inhibition screening of monoamine oxidase (HMAO-B IC_{50}= 0.083± 0.001 M, HMAO-A IC_{50}= 6.11 ± 0.08µM; SI=73.5) and prediction of blood-brain barrier permeability.[25]

Ornella *et al*. 2016 synthesized N1- and C5-substituted 1,2,3-triazole derivatives by coupling various azides and alkynes through Cu-catalyzed 1,3-dipolar Huisgen cycloaddition. All of the synthetic compounds underwent testing against MAO-A and MAO-B. To understand the binding affinities and selectivity between two enzyme isoforms, structure-activity correlations, and molecular modeling were employed. The results showed that compounds **33, 36, and 84** containing the 4-triazolyl alkyl propargylamine scaffold are a good starting point for investigating the development of multipotent anti-Alzheimer drugs with irreversible MAO-B inhibitory action. 2D structures of these compounds were mentioned in **Figures 1p, 1q, and 1r.**[26]

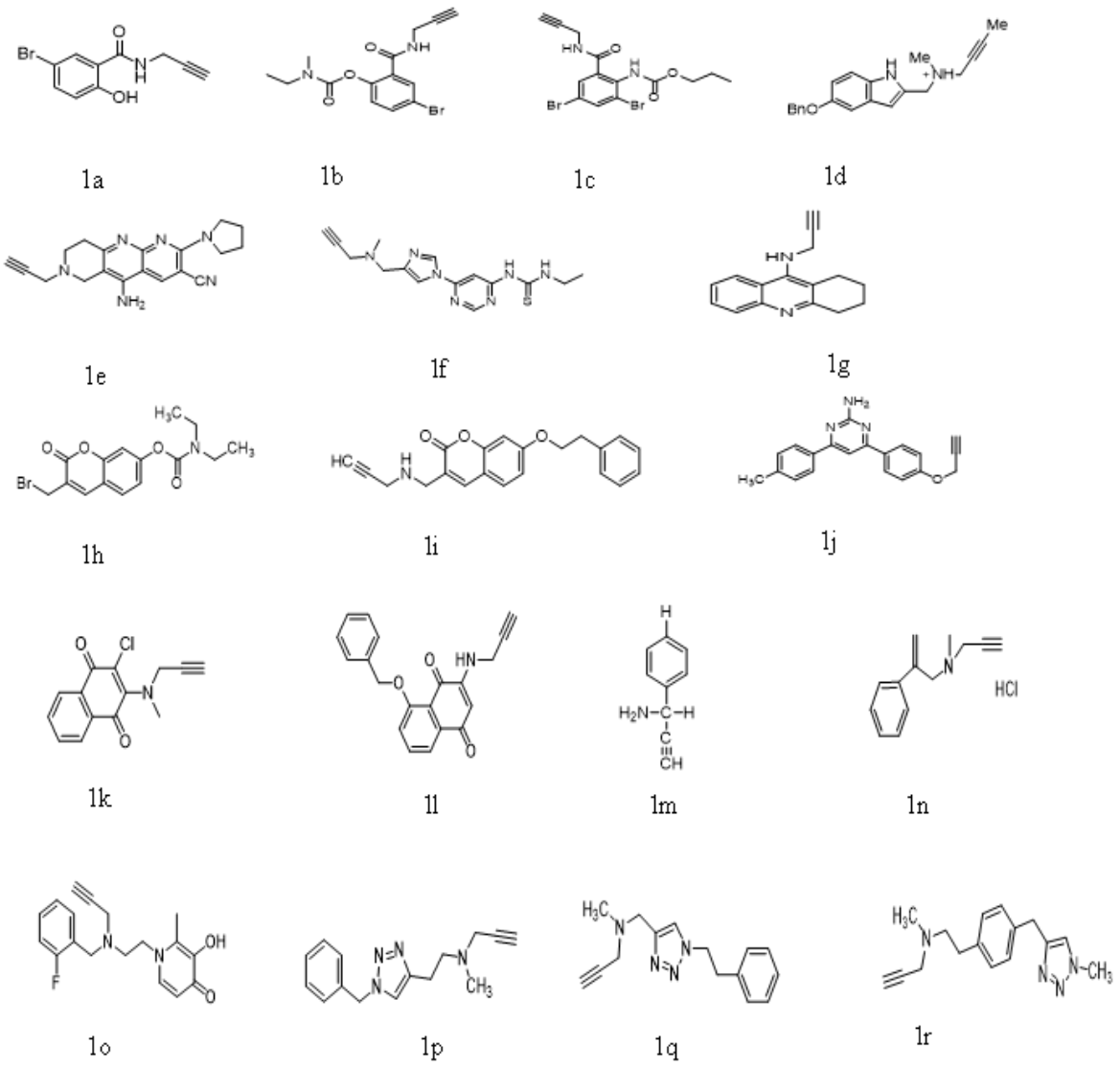


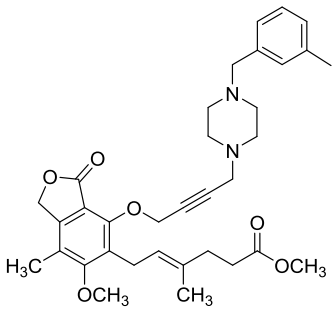
Figure 1: 2D images of Neuro protective agents.

Cytotoxic activity

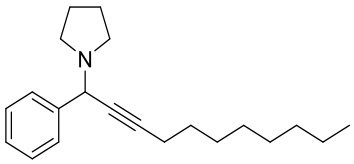
P. Silalai *et al*. 2021, designed and synthesized twenty-six propargylamine mycophenolate analogs from mycophenolic acid 1 utilizing a key step A3-coupling reaction. Six cancer cell lines were tested for cytotoxic efficacy against these. In contrast to the lead chemical, MPA 1, and a reference medicine, ellipticine, the study found that the compounds 6a, 6j, 6t, 6u, and 6z demonstrated preferential cytotoxicity towards neuroblastoma (SH-SY5Y) cancer cells and were less hazardous to normal cells. Molecular docking experiments showed that compound **6a (Figure 2a)** fit well in the essential amino acids of three proteins that are potential targets for cancer therapy: CDK9, EGFR, and VEGFR-2. According to the research, the scaffold of propargylamine mycophenolate could be a useful place to start when creating novel neuroblastoma anticancer medications.[9]

Martinez-Amezaga *et al.* 2020 synthesized a series of 1-substituted propargylic tertiary amines using the A3-coupling reaction. A cell viability experiment was then used to assess the potential of the produced propargylamine derivatives. Pancreatic cancer PANC-1 cells and triple-negative breast cancer 4T1 cells were used in the experiment to measure the inhibitory effect against these particular cancer types. The researchers inferred from the experiment observations that compound **11b** showed a selectivity index larger than 3 for triple-negative breast cancer cells. Additionally, compound **18a** shows a fascinating selectivity for pancreatic cancer cells of 41.17. These levels of selectivity suggest the compounds' potential as excellent candidates for the creation of novel chemotherapeutic anticancer drugs. To fully explore the potential of these substances and to maximize their efficacy as prospective therapies for pancreatic and breast cancer, additional research and development are necessary. 2D structures of the 2 potent molecules were mentioned in **Figure 2b, 2c.**[27]

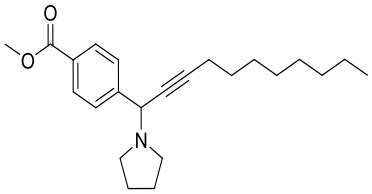
In research, **Kadela-Tomanek *et al.* 2017** produced 5,8-quinolinedione derivatives by adding acetylenic amine groups. Then, these substances were examined utilizing a variety of analytical methods, including 1H and 13C NMR, IR spectroscopy, and MS spectra. The cytotoxic effects of these synthetic chemicals on three human cancer cell lines were also assessed by the researchers. Derivatives 2a-c and 3a-c from the chemicals they produced showed more cytotoxic activity than the standard substance cisplatin towards the C-32 (melanoma cell line) and T47D (breast cancer cell line). According to the findings, a triple connection was essential for the activity to be seen. Additionally, the cytotoxic action against the melanoma (C-32) and breast cancer (T47D) cell lines were followed by N-methylpropargylamine, 1,1-dimethylpropargylamine, and propargylamine in compounds containing acetylenic amine substituents. It's interesting that the researchers discovered a reduction in cytotoxic activity when the length of the acetylenic amine chain was extended by the addition of methyl groups. 2D structure of compound 2a was mentioned in the **Figure 2d.**[28]



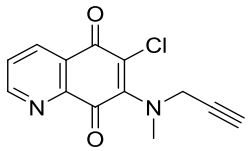
2a



2b



2c



2d

Figure 2: 2D structures of cytotoxic agents.

2.3 Anti-Oxidant activity

Yeray *et al*. 2019 A novel series of N-propargyl tetrahydroquinolines 6a-g were synthesized from *N*-propargylanilines, formaldehyde, and N-vinylformamide through the cationic Povarov reaction (a domino Mannich/Friedel-Crafts reaction). All the tetrahydroquinoline derivatives were tested in vitro to neutralize free radicals. Among all the synthesized compounds, compound **6c** showed potent anti-oxidant activity, the 2D structure was mentioned in **Figure 3a.**

Kochman *et al.* 2003 synthesized a group of nitroxyl N-propargylamine derivatives known as "JSAKs." Two chosen JSAK compounds, together with the parent nitroxyl, were examined in vitro to determine their reactivity and antioxidative efficacy against reactive oxygen species (ROS). According to the experimental findings, **JSAK-641 (Figure 3b)**, one of the developed compounds, has more antioxidative effectiveness than the reference chemical deprenyl (DEP). The study's findings suggest that free radicals, which are linked to neurodegenerative diseases like PD, may be inhibited by these synthetic compounds. Due to their potential as therapeutic agents for the treatment of such illnesses, these compounds necessitate further study.[29]

Dragoni *et al.* 2006 conducted a study to evaluate the antioxidant properties of propargylamine derivatives, as reported by Messina et al. One of the substances examined, 1-phenylpropargylamine (AP3), showed concentration-dependent suppression of ONOO-induced dichlorofluorescin and linoleic acid oxidation. When AP3 was in contact with peroxynitrite, its UV-visible absorbance characteristics showed spectrum alterations, which suggested the emergence of a new substance. The chemical in query was identified as phenylpropargyl alcohol via a gas chromatograph-mass spectrometer study. The aminopropargyl moiety and the availability of the electron pair on the nitrogen atom were found to be the two factors that contributed to AP3's capacity to scavenge free radicals, according to an analysis of the structure-activity connection. Based on these discoveries, it was proposed that AP3**(Figure 3c)** may be used as a lead chemical in the synthesis of novel derivatives that have ONOO-scavenging capabilities.[30]

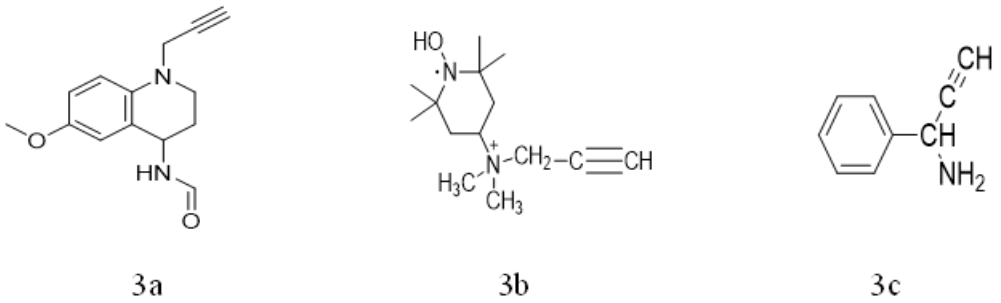


Figure 3: 2D images of anti oxidant agents.

2.4 Cardioprotective activity

Kleiner *et al*. 2008 studied the cardioprotective activity of well-known neuroprotective compounds TVP1022 and propargylamine. The research involved testing newborn rat ventricular myocytes (NRVM) for apoptosis brought on by serum deprivation and the anthracycline chemotherapy drug doxorubicin. The study showed that pretreatment of NRVM cultures with TVP1022, or propargylamine, stopped the increase in cleaved caspase 3 levels, and reversed the reduction in the Bcl-2/Bax ratio. This attenuated doxorubicin-induced and serum starvation-induced apoptosis. The study reported that the propargylamine moiety is responsible for its cytoprotective nature. The study also showed that the compound did not interfere with the anticancer activity of Doxorubicin. The research also recommended that TVP1022, which may be given in conjunction with doxorubicin to treat human malignancies, be taken into consideration as a new cardio-protective drug against ischemia shocks and anthracycline cardiotoxicity.[8]

2.5 Antimicrobial activity

Pankaj *et al*. 2018 studied antimicrobial activity of propargylamine derivatives of mercaptobenzoxazole and oxazolo [4,5-b]pyridine-2-thiol derivatives 7a-7h were examined. The sequential reaction of 2-aminophenol/2-aminopyridin-3-ol with CS2, followed by alkylation and addition reaction with secondary amines and formaldehyde has been used to create propargylamine derivatives. It occurs at room temperature in the presence of CuI. Testing was done on all the synthetic chemicals to see if they could stop the replication of bacteria like *E. coli, P. aeruginosa*, *S. aureus*, and *S. pyrogens* as well as harmful fungi like *C. albicans, A. niger*, and *A. clavatus*.[10]

CONCLUSION

From an extensive literature search on the propargylamine moiety, it becomes evident that propargylamine and its derivatives hold significant promise as therapeutic agents in the domain of drug discovery. They have demonstrated remarkable potential in addressing neurodegenerative disorders, particularly AD and PD. The key mechanisms of action involve the inhibition of MAO-A and MAO-Bisoforms and AChE. Propargylamine derivatives, such as rasagiline and selegiline, have already gained approval for the treatment of PD by targeting MAO-B inhibition. Furthermore, the multifaceted nature of propargylamine derivatives extends beyond neurodegenerative disorders. They have demonstrated diverse pharmacological activities, including antioxidant, anticancer, antimicrobial, cardioprotective, and cytotoxic properties. The antioxidant activity of these derivatives contributes to their neuroprotective efficacy by counteracting oxidative damage and promoting cellular health. By providing a comprehensive overview of these pharmacological activities and highlighting the most promising molecules from various studies, this review serves as a valuable resource for medicinal chemists. It enables the identification and exploration of potential propargylamine derivatives for further development and optimization as therapeutic agents. The emergence of propargylamine as a pivotal moiety in drug discovery signifies its growing importance in the search for innovative treatment strategies. The multifunctional nature of propargylamine derivatives, combined with their demonstrated efficacy in various therapeutic areas, underscores their potential for making substantial contributions to the development of novel and effective medications. Continued research and development in this field hold the key to unlocking the full therapeutic potential of propargylamine and paving the way for the discovery of novel drugs that can improve the lives of patients suffering from debilitating neurological conditions.

ABBREVIATIONS

AD: Alzheimer's Disease

PD: Parkinson’s Disease

MpTp: Mitochondrial permeability Transition pore

AChE: Acetylcholinesterase

BuChE: Butyrylcholinesterase

MAO-A/B: MonoAmino Oxidase A/B

MTDLs: Multi-Target-Directed Ligands

SAR: Structure-Activity Relationship

REFERENCES

1. Lauder K, Toscani A, Scalacci N, Castagnolo D. Synthesis and reactivity of propargylamines in organic chemistry. Chem Rev., 2017; 117: 14091–14200**.**
2. Zhao F, Kim S, Castagnolo D. Propargylamines: Recent Advances in Asymmetric Synthesis and Use as Chemical Tools in Organic Chemistry. Methodologies in Amine Synthesis: Challenges and Applications, 2021; 103–154.
3. Ghosh S, Biswas K. Metal-free multicomponent approach for the synthesis of propargylamine: A review. RSC Adv., 2021; 11: 2047–2065**.**
4. Mandlimath TR, Sathiyanarayanan KI Facile synthesis of ZnAl 2 O 4 nanoparticles: efficient and reusable porous nano ZnAl 2 O 4 and copper supported on ZnAl 2 O 4 catalysts for one pot green synthesis of propargylamines and imidazo [1, 2-a] pyridines by A 3 coupling reactions. RSC Adv., 2016; 6: 3117–3125**.**
5. Zindo FT, Malan SF, Omoruyi SI, Enogieru AB, Ekpo OE, Joubert J. Design, synthesis and evaluation of pentacycloundecane and hexacycloundecane propargylamine derivatives as multifunctional neuroprotective agents. Eur J Med Chem., 2019; 163: 83–94**.**
6. Youdim MBH, Bar Am O, Yogev-Falach M, Weinreb O, Maruyama W, Naoi M, Amit T. Rasagiline: neurodegeneration, neuroprotection, and mitochondrial permeability transition. J Neurosci Res., 2005; 79: 172–179**.**
7. Cavalli A, Bolognesi ML, Minarini A, Rosini M, Tumiatti V, Recanatini M, Melchiorre C. Multi-target-directed ligands to combat neurodegenerative diseases. J Med Chem., 2008; 51: 347–372**.**
8. Kleiner Y, Bar-Am O, Amit T, Berdichevski A, Liani E, Maor G, Reiter I, Youdim MBH, Binah O. TVP1022 and propargylamine protect neonatal rat ventricular myocytes against

doxorubicin-induced and serum starvation-induced cardiotoxicity. J Cardiovasc Pharmacol., 2008; 52: 268–277.

9. Silalai P, Pruksakorn D, Chairoungdua A, Suksen K, Saeen R. Synthesis of propargylamine mycophenolate analogues and their selective cytotoxic activity towards neuroblastoma SH-SY5Y cell line. Bioorg Med Chem Lett., 2021; 45: 128135**.**
10. Gour PB, Rajani DP Synthesis of propargylamine derivatives of benzo[d]oxazole-2-thiol/oxazolo[4,5-b]pyridine-2-thiol as Antimicrobial agents, 2018.
11. Krátký M, Vu QA, Štěpánková Š, Maruca A, Silva TB, Ambrož M, Pflegr V, Rocca R, Svrčková K, Alcaro S. Novel propargylamine-based inhibitors of cholinesterases and monoamine oxidases: Synthesis, biological evaluation and docking study. Bioorg Chem., 2021; 116: 105301**.**
12. Samadi A, De Los Ríos C, Bolea I, Chioua M, Iriepa I, Moraleda I, Bartolini M, Andrisano V, Gálvez E, Valderas C. Multipotent MAO and cholinesterase inhibitors for the treatment of Alzheimer's disease: synthesis, pharmacological analysis and molecular modeling of heterocyclic substituted alkyl and cycloalkyl propargyl amine. Eur J Med Chem., 2012; 52: 251–262.
13. Zindo FT, Malan SF, Omoruyi SI, Enogieru AB, Ekpo OE, Joubert J. Design, synthesis and evaluation of pentacycloundecane and hexacycloundecane propargylamine derivatives as multifunctional neuroprotective agents. Eur J Med Chem., 2019; 163: 83–94**.**
14. Xu Y, Wang H, Li X, Dong S, Liu W, Gong Q, Tang Y, Zhu J, Li J, Zhang H. Discovery of novel propargylamine-modified 4-aminoalkyl imidazole substituted pyrimidinylthiourea derivatives as multifunctional agents for the treatment of Alzheimer's disease. Eur J Med Chem., 2018; 143: 33–47**.**
15. Mao F, Li J, Wei H, Huang L, Li X Tacrine–propargylamine derivatives with improved acetylcholinesterase inhibitory activity and lower hepatotoxicity as a potential lead compound for the treatment of Alzheimer's disease. J Enzyme Inhib Med Chem., 2015; 30: 995–1001**.**
16. Zindo FT, Barber QR, Joubert J, Bergh JJ, Petzer JP, Malan SF Polycyclic propargylamine and acetylene derivatives as multifunctional neuroprotective agents. Eur J Med Chem., 2014; 80: 122–134**.**
17. Mzezewa SC Synthesis and evaluation of 7-substituted 3-propargylamine coumarin derivatives as multifunctional monoamine oxidase and cholinesterase inhibitors for Alzheimer's Disease treatme, 2020.

18. Kumar B, Kumar M, Dwivedi AR, Kumar V. Synthesis, Biological Evaluation and Molecular Modeling Studies of Propargyl-Containing 2, 4, 6-Trisubstituted Pyrimidine Derivatives as Potential Anti-Parkinson Agents. Chem MedChem., 2018; 13: 705–712.
19. Maruyama W, Weinstock M, Youdim MBH, Nagai M, Naoi M. Anti-apoptotic action of anti-Alzheimer drug, TV3326 [(N-propargyl)-(3R)-aminoindan-5-yl]-ethyl methyl carbamate, a novel cholinesterase-monoamine oxidase inhibitor. Neurosci Lett., 2003; 341: 233–236.
20. Yogev-Falach M, Amit T, Bar-Am O, Youdim MBH The importance of propargylamine moiety in the anti-Parkinson drug rasagiline and its derivatives for MAPK-dependent amyloid precursor protein processing. The FASEB journal., 2003; 17: 2325–2327.
21. Mezeiova E, Janockova J, Andrys R, Soukup O, Kobrlova T, Muckova L, Pejchal J, Simunkova M, Handl J, Micankova P. 2-Propargylamino-naphthoquinone derivatives as multipotent agents for the treatment of Alzheimer's disease. Eur J Med Chem., 2021; 211: 113112.
22. Nag S, Kettschau G, Heinrich T, Varrone A, Lehmann L, Gulyas B, Thiele A, Keller É, Halldin C. Synthesis and biological evaluation of novel propargyl amines as potential fluorine-18 labeled radioligands for detection of MAO-B activity. Bioorg Med Chem., 2013; 21: 186–195.
23. Yu PH, Davis BA, Boulton AA Aliphatic propargylamines: potent, selective, irreversible monoamine oxidase B inhibitors. J Med Chem., 1992; 35: 3705–3713.
24. Baranyi M, Porceddu PF, Gölöncsér F, Kulcsár S, Otrokocsi L, Kittel Á, Pinna A, Frau L, Huleatt PB, Khoo M-L Novel (Hetero) arylalkenyl propargylamine compounds are protective in toxin-induced models of Parkinson's disease. Mol Neurodegener., 2016; 11: 1–21.
25. Guo J, Zhang Y, Zhang C, Yao C, Zhang J, Jiang X, Zhong Z, Ge J, Zhou T, Bai R. N-propargylamine-hydroxypyridinone hybrids as multitarget agents for the treatment of Alzheimer's disease. Bioorg Chem., 2021; 113: 105013.
26. Di Pietro O, Alencar N, Esteban G, Viayna E, Szałaj N, Vázquez J, Juárez-Jiménez J, Sola I, Pérez B, Solé M. Design, synthesis and biological evaluation of N-methyl-N-[(1, 2, 3-triazol-4-yl) alkyl] propargylamines as novel monoamine oxidase B inhibitors. Bioorg Med Chem., 2016; 24: 4835–4854.
27. Martinez-Amezaga M, Giordano RA, Gori DNP, Squizatto CP, Giolito M V, Scharovsky OG, Rozados VR, Rico MJ, Mata EG, Delpiccolo CML Synthesis of propargylamines via

the A 3 multicomponent reaction and their biological evaluation as potential anticancer agents. Org Biomol Chem., 2020; 18: 2475–2486**.**

28. Kadela-Tomanek M, Jastrzębska M, Bębenek E, Chrobak E, Latocha M, Kusz J, Tarnawska D, Boryczka S. New acetylenic amine derivatives of 5, 8-quinolinediones: Synthesis, crystal structure and antiproliferative activity. Crystals (Basel), 2017; 7: 15**.**
29. Kochman A, Skolimowski J, Gêbicka L, Metodiewa D. Antioxidant properties of newly synthesized N-propargylamine derivatives of nitroxyl: a comparison with deprenyl. Pol J Pharmacol, 2003; 55: 389–400**.**
30. Dragoni S, Porcari V, Valoti M, Travagli M, Castagnolo D. Antioxidant properties of propargylamine derivatives: assessment of their ability to scavenge peroxynitrite. Journal of pharmacy and pharmacology, 2006; 58: 561–565.