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TRIAZOLE CONTAINING HETEROCYCLIC COMPOUND AS POTENTIAL THERAPEUTIC AGENTS FOR PARKINSON'S DISEASE-A REVIEW

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ABSTRACT: Parkinsonism is a neurodegenerative disease caused by the loss of dopaminergic neurons in substantia nigra par compacta region. The review is to summarize various triazole containing heterocyclic compounds having anti parkinsonism activity and their synthesis. Studies in heterocyclic compounds are now important due to its wide variety of pharmacological activity. This is a broad compilation of works carried out in the past decades on triazole containing heterocyclic compounds. This scaffold is now explored by researchers for developing novel potential drug molecules. Triazole containing compounds have the potential activity on the neurodegenerative diseases like Parkinson's disease.

KEYWORDS: Parkinsonism, Triazole, Heterocyclic Compounds, Dopamine, Oxidative Stress, Antioxidant activity, Alpha-synuclein, MAO-B Inhibitors, Neuroprotection.

ABBREVIATION:

PD – Parkinson Disease, ROS- Reactive oxygen species, DA -Dopamine, DAQ-Dopamine Quinones, MAO-B -Monoamine Oxidase B, COMT - Catechol -O -Methyl Transferase, 6 -OHDA- 6-hydroxydopamine, FRET-fluorescence resonance energy transfer

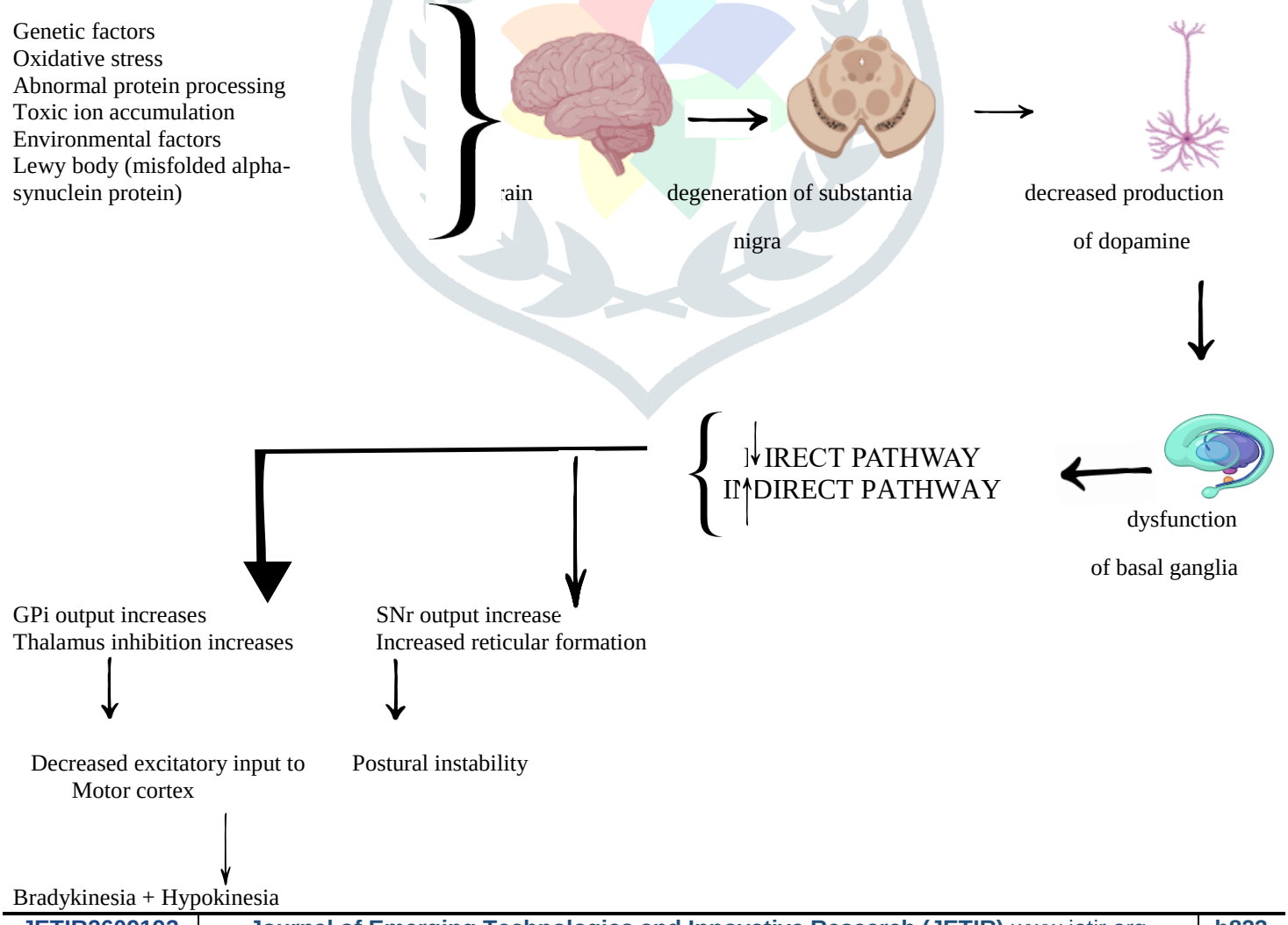
INTRODUCTION

Parkinsonism disease (PD) is a chronic, progressive neurodegenerative disease that is associated with loss of dopaminergic neurons in the substania nigra of the brain and the formation of Lewy bodies in affected brain area or Lewy neurites formed by the aggregation of disordered protein alpha synuclein [1,2]. This syndrome is described by James Parkinson in 1817 in his 'Essay on shaking Palsy' which is commonly referred to as Parkinson disease. [3]

Due to the depletion of dopaminergic neurons in the substantia nigra, the balance between direct and indirect pathway gets impaired. The direct pathway is mediated by D1 receptor and indirect pathway is mediated by D2 receptor [4]. Dopamine acts on D1 receptor results in excitation of striatal neurons and inhibition of internal globus pallidus and substantia nigra pars reticulate [5]. Therefore cortex is excited by thalamus which initiating movements. In the indirect pathway dopamine act on D2 receptors [6] thereby inhibit globus pallidus externus and which send inhibitory signals to thalamus and inhibit unwanted movements. The destruction of dopaminergic neurons [7] cause the imbalance of direct and indirect pathway. As a result underactivation of direct pathway and overactivation of indirect pathway takes place and which causes inhibition of thalamus [8] which leads to decreased excitatory input to cortex and it results bradykinesia and hypokinesia like motor symptoms. Loss of dopaminergic neurons also leads to the formation of lewybodies [9] and it results dementia [10] and cognitive impairment.

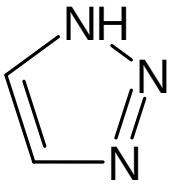
Oxidative stress also plays a major role in dopaminergic neurotoxicity [11]. The metabolism of endogenous dopamine (DA)induces oxidative stress in dopaminergic neuron. DA may undergo auto-oxidation or metabolism by enzymes or metal ions. Reactive oxygen species (ROS), DA quinones (DAQs) and 3,4-dihydroxyphenylacetaldehyde (DOPAL) are the toxic DA metabolites [12,13].

The consequent decrease in striatal dopamine is the neurochemical underlying of Parkinson's disease, the development of Parkinson motor symptoms appears to be dependent upon adequate for the impairment of striatal dopaminergic transmission [14]. Cardinal motor symptoms include bradykinesia, tremor, muscle rigidity, postural instability and non-motor symptoms include anosmia, hypophonia, sleep problems, depression and cognitive changes [15,16]. Tremor is one of the major symptoms of parkinsonism and it occur in 75 percent of patients, mainly at the time of disease onset [17].

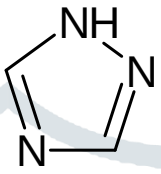


Numerous risk factors include age, gender, ethnicity, rapid eye movement, sleep disorder, high dairy consumption, traumatic brain injury, genetics and pesticides/herbicides are known to contribute to development of parkinson disease [18]. Levodopa/Carbidopa is the most effectively used drug. Other drugs include DA agonist (bromocriptine, cabergoline,), Monoamine oxidase B (MAO-B) inhibitors (selegiline, rasagiline), Catechol-O-methyl transferase (COMT) inhibitors (tolcapone, entacapone), anti-cholinergics (benzhexol), and amantadine [19]. But these drugs have side effects like dyskinesia, wearing off phenomenon, hepatotoxicity, cognitive impairment and Neuropsychiatric effect [20].

Triazole and its derivatives has got great attention in past few years due to its wide variety of pharmacological activity and its structural activity relationship are studied [21]. These compounds especially 1,2,3 and 1,2,4 triazole derivatives have antimicrobial, antioxidant, anticonvulsant, antiviral, antineoplastic and anti alzheimers activities [22,23].

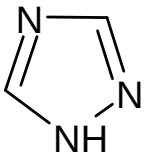


1,2,3-triazole

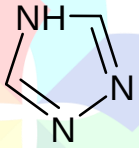


1,2,4-triazole

Triazoles are also known as pyrrodiazoles and they are one of the important heterocyclic compounds having five membered di-unsaturated ring structure. Its molecular formula is C2H3N3. There are 2 isomeric forms, 1,2,3 and 1,2,4-triazoles [24]. There 2 tautomeric forms for 1,2,4-triazoles, 1H-1,2,4-triazole and 4H-1,2,4-triazole. And among them 1H is most one [25].

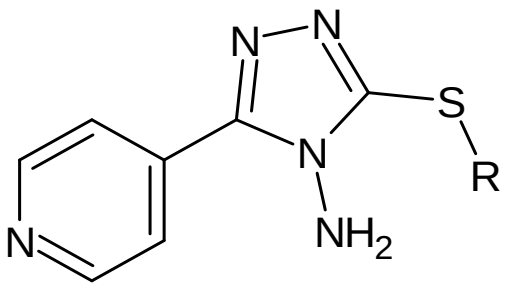


1H-1,2,4-triazole



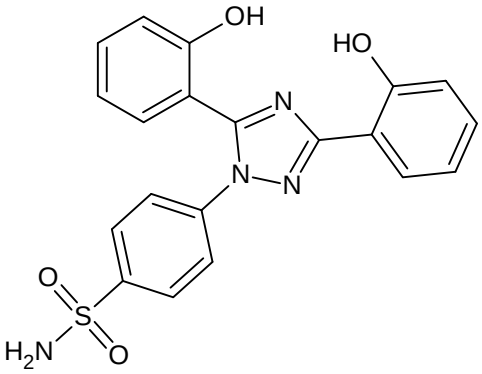
4H-1,2,4-triazole

Among the azoles, triazoles are the most stable ones [25]. In recent years, studies show that compounds having 1,2,4-triazole have activity against the alpha-synuclein aggregation which is one of the major cause of parkinsonism. These compounds are newly synthesized by Rosaria et al. and it undergo *invitro* and *invivo* studies. The studies shows that, it significantly reduces the aggregation of alpha-synuclein. From a set of 4-amino-5–(4-pyridinyl)-4*H*-1,2,4-triazole-derived compounds, we identified the 3-(cinnamylsulfanyl)-5-(4-pyridinyl)-1,2,4-triazol-4-amine that proved to reduce α-syn aggregation in an in vitro assay [26].



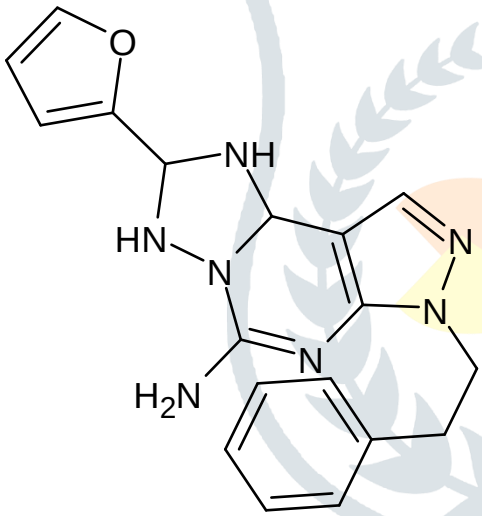
R=H, -CH2CH3, -CH2COOCH3, -CH2COOCH2CH3 [26]

Xuan liu et al. were designed and synthesised a number of 1,3,5-triphenyl -1,2,4-triazole derivatives using combinations of principle,and they demonstrated that SYS18 is the best compound with effective anti oxidative stress action [27].



[27]

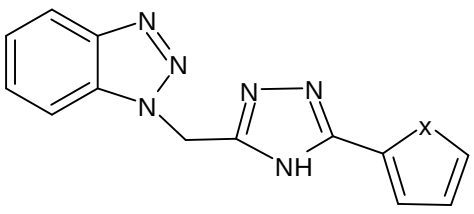
Ongini et al. investigated a few heterocyclics and they replace the phenyl ring in CGS 15943 with heterocyclics like pyrazole or imidazole which gives compound having A2a receptor inhibiting activity (SCH 58261) [22].



(2-(furan-2-yl)-7-(2-phenylethyl)-2,3,7,9b-tetrahydro-1H-pyrazolo [4,3- e][1,2,4] triazolo[1,5-c]pyrimidin-5-amine)

Studies shown that 1,2,4 triazole derivatives have antioxidant activity. Among them [1,2,4] triazolo[1,5-a] pyridine derivatives have specific antioxidant activity. Its activity depends upon their chemical structure. 7-bromo- and 5-bromo- [1,2,4] trozolo[1,5-a] pyridines are observed having highest antioxidant activity [28].

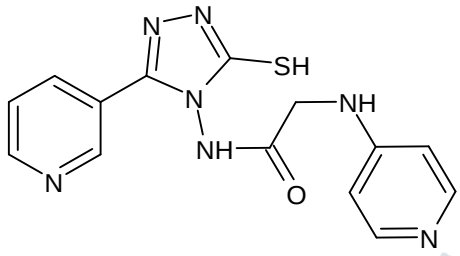
CHAND et al. synthesis a few new molecules of 1-(((aryl)3-yl)-4H-(1,2,4)-triazol-5-ylmethyl)-1H-benzotriazoles and they report that it has antimicrobial and antioxidant activity. The antimicrobial activity is evaluated by cup plate method and is assessed by measuring zone of inhibition. The antioxidant activity is evaluated by 2,2-diphenyl-1-picrylhydrazyl radical assay (DPPH) [29].



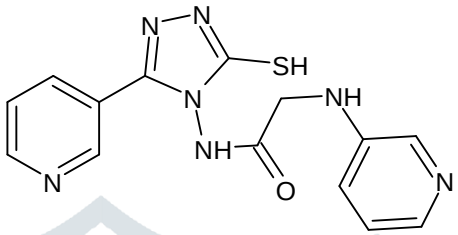
X=O, X=S

They synthesize 1,2,4-triazole by mixing acetohydrazide and substituted aromatic aldehyde/ heteroaromatic aldehyde (1:1) by dissolving in a minimum quantity of acetic acid. Then ammonium acetate is added and sit in room temperature. After completing the reaction, the contents are poured on ice cold water and neutralize using ammonia [29].

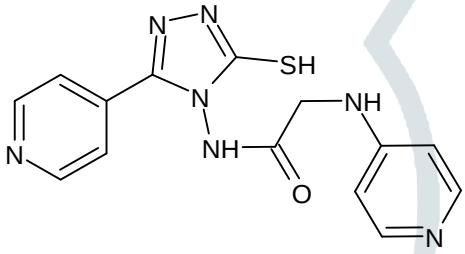
Suresh et al. synthesise some new Amino derivatives of 5-Aryl-4-(chloroacetylamio)-3-mercapto-4H-1,2,4-triazole. It shows that these newly synthesized compounds has got antimicrobial activity, it is evaluated by agar-well diffusion method [30].



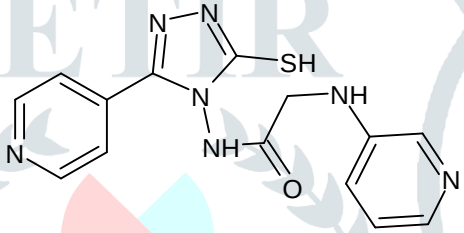
A



B



C



D

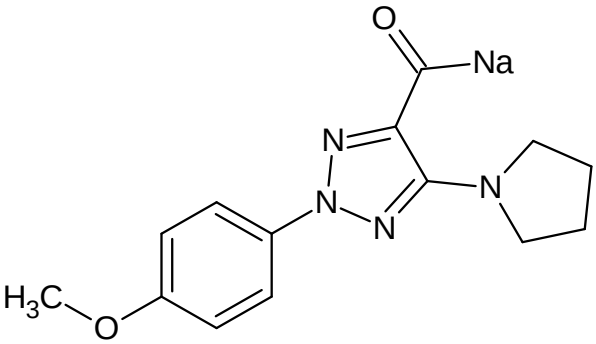
They synthesize these new derivatives by a 7step synthesis scheme. First they synthesize ester from acid followed by synthesizing hydrazide and potassium dithiocarbazinate. By refluxing dithiocarbazinate with hydrazine hydrate and water resulting in the formation of 5-Aryl-4-amino-3-mercapto-4H-1,2,4-triazole followed by reflux with benzene to produce the derivatives [30].

Roman SCHERBYNA synthesis derivatives of 4-substituted-3-(morpholinomethyl)-4H-1,2,4-triazole-5-thioles by microwave assisted technique. He synthesize it from 4-R1-3-(morpholinomethyl)-4H-1,2,4-triazole-5-thiol with (bromomethyl)cyclohexane and 2-chloropyridine using the Milestone Flex Wave microwave synthesis system.The structure is analysed by NMR spectroscopy,elemental analysis and gas chromatography-mass spectroscopy(GS/MS) [31].

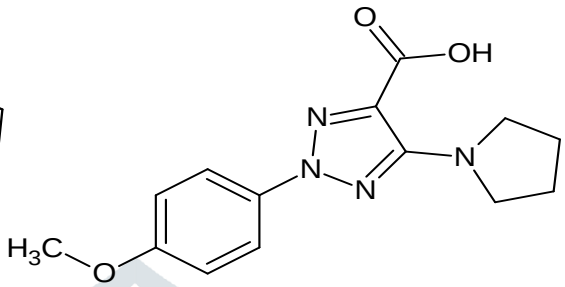
1,2,3-triazole, a five-membered heterocyclic ring, a central scaffold, and is capable of interacting with a variety of receptors and enzymes to exhibit a broad range of important biological activities. They are vital for treating a wide variety of diseases, including antibacterial, antifungal, antitubercular, antiviral, anti-Alzheimer's, anticancer, antiparasitic, antidiabetic and anti parkison. It act as a potent inhibitor of acetylcholinesterase. Due to AchE inhibitor activity 1,2,3-triazole derivatives increases the level of acetylcholine it has role in symptomatic treatment in Parkinson like neurodegenerative diseases. They are mainly used to treat Parkinson disease dementia(PDD) and associated cognitive defecits [32].

Its chemical stability, dipole moment, and ability to involve in hydrogen bonding make it an important building block for novel biologically active chemical species. Oxidative stress is one of the major mechanism which cause damage and death of brain cells ,especially dopamine producing neurons; which is a contributing factor to parkinsonism.so the antioxidant property of 1,2,3- triazole derivatives have an essential role in Parkinson treatment [33,34]. An in-vitro investigation of the impact of two triazole derivatives -sodium 2-(4-methoxyphenyl)-5-(pyrrolidin-1-yl)-2H-1,2,3-triazole-4-carboxylate and 2-(4-methoxyphenyl)-5-(pyrrolidin-1-

yl)-2H-1,2,3-triazole-4-carboxylic acid (named BNP02 and BNP04, respectively) show antioxidant property [34].

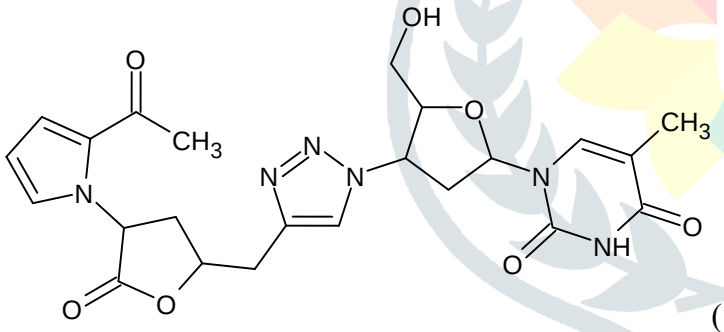


BNP02



BNP04

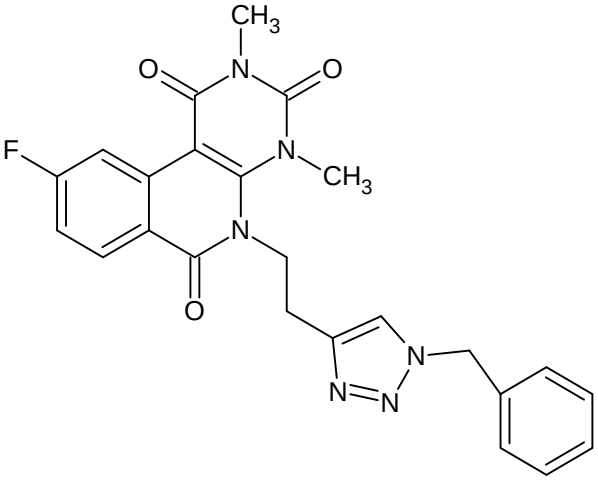
One of the most difficult areas of current medical research for the creation of treatments for neurological conditions like Parkinson's and Alzheimer's disease is neuroprotection. In recent years, the design, synthesis, and modification of neuroprotective medicines based on 1,2,3-triazole-linked hybrids has continued to be a significant area of research. For possible increased neurotrophic action, 1,2,3 triazoles including longanlactone analogues were synthesized.



(105)

A series of cell-based and neurite outgrowth tests verified that the above 1,2,3-triazole-containing derivative showed significant neurotrophic activity in Neuro-2a cells [34].

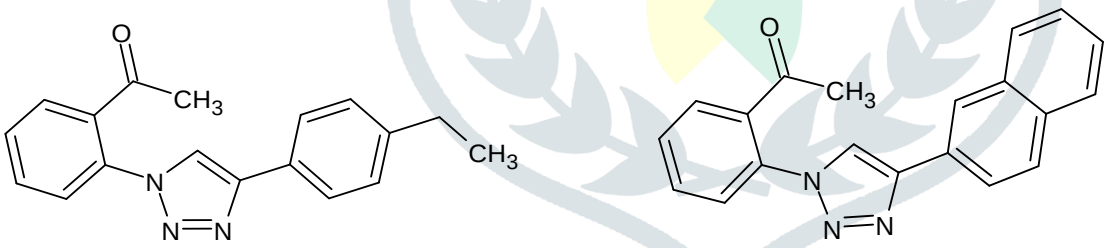
For antioxidant screening, a number of novel functionalized 1,2,3-triazole-pyrimido[4,5-c] isoquinolines were created [34].



(126)

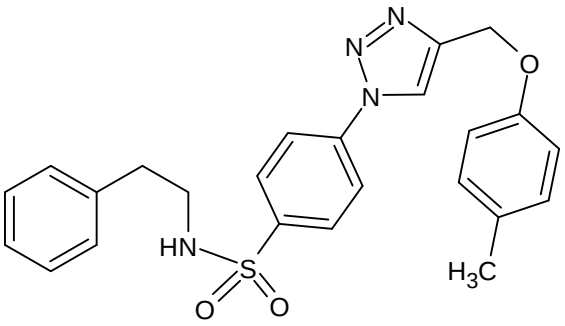
The above demonstrated derivative have stronger antioxidant potency with an IC50 value of 6.02µM than the positive control drug Trolox (1.94-fold higher activity than the positive control drug Trolox), according to an in vitro antioxidant activity analysis using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. It should be mentioned that the most common derivatives with linked electron-withdrawing substituents (such as F, Cl, and NO2) in the pyrimidoisoquinoline system and triazole moiety demonstrated average to excellent antioxidant properties [34].

Monoamine oxidases (MAOs) are enzymes responsible for the degradation of neuroactive amines, like dopamine, a neurotransmitter essential for motor, cognitive, and behavioral functions. Among these, MAO-B is essential for dopamine metabolism, generating oxidative species and reactive metabolites that fuel the oxidative stress linked to Parkinson's disease pathogenesis. Therefore MAO inhibition is an essential treatment strategy for prevent dopamine metabolism. Costa and co-workers performed in silico, synthetic, and biological studies with a family of 2′ -(1,2,3-triazol)-acetophenones, leading to the identification of these compounds mentioned below; 185a (IC50 MAO-A = 2.64 µM,) and 185b (IC50 MAO-B = 41.47 µM), as interesting selective MAO-A and MAO-B inhibitors, respectively [35].

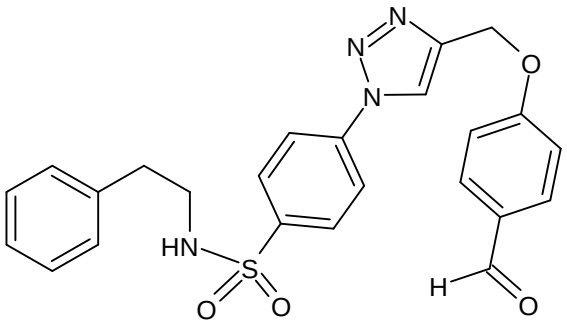


185a 185b

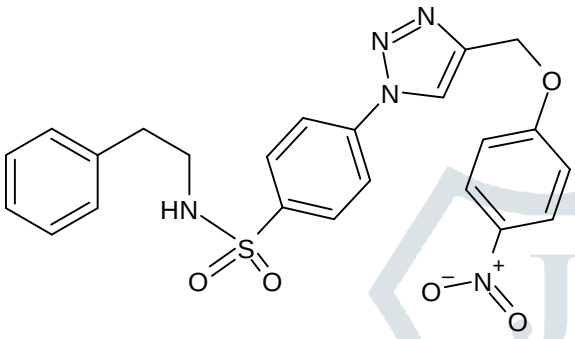
A potent neurotoxin called 6-hydroxydopamine (6-OHDA) selectively damages dopaminergic neurons in the brain, mainly in the nigrostriatal pathway, to produce animal models of Parkinson's disease. It helps in drug testing and research by simulating both non-motor symptoms like cognitive decline and motor symptoms like tremors and decreased mobility. The protective effects of these triazole derivatives against 6-hydroxydopamine (6-OHDA)-induced neurotoxicity in the neuroblastoma SH-SY5Y cell line were examined. These results demonstrated that in 6-OHDA-induced SH-SY5Y neuronal cells, the chosen 1,2,3-triazole-based sulfonamide derivatives successfully decreased oxidative stress by lowering intracellular ROS generation. The selected derivatives are given below [36].



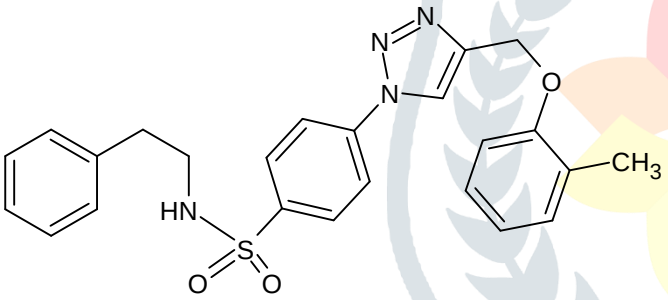
2a



3a

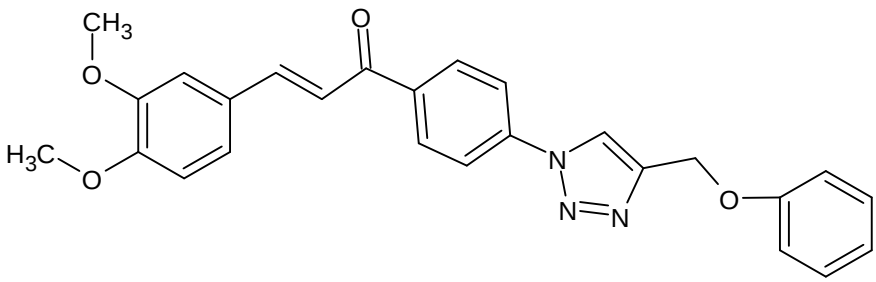


4a

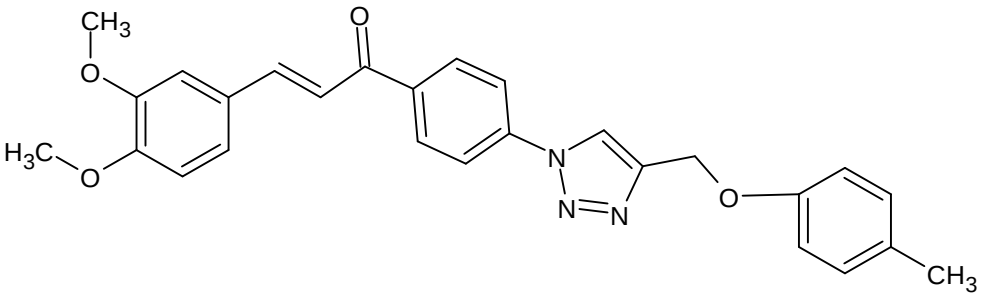


5a

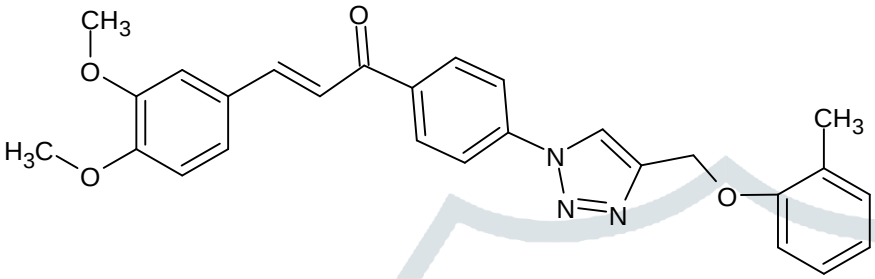
Various studies shown that 1,2,3- triazole coupled with many bioactive compounds like quinolone [37], triazine [38], chromenone [39] lipoic acid [40] and tacrine [41] are useful to treat neurodegenerative disorders. Pichjira et al. were synthesized chalcone- triazole hybrids (6a-g) and evaluated their anti-apoptosis, antioxidant and molecular mechanism underlying neuroprotection [42].



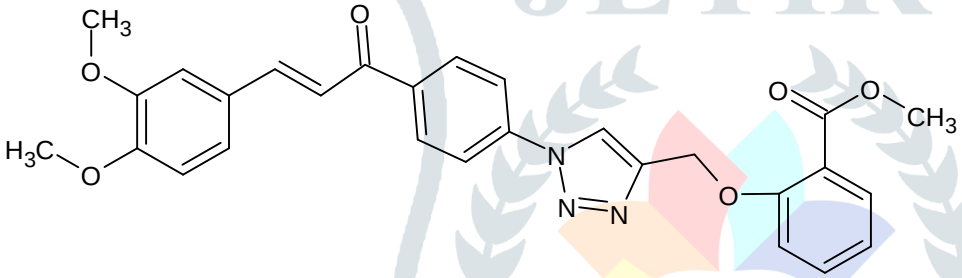
6a



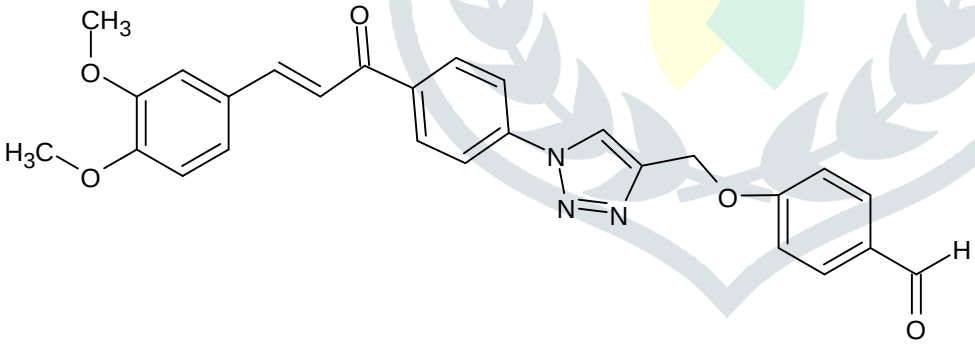
6b



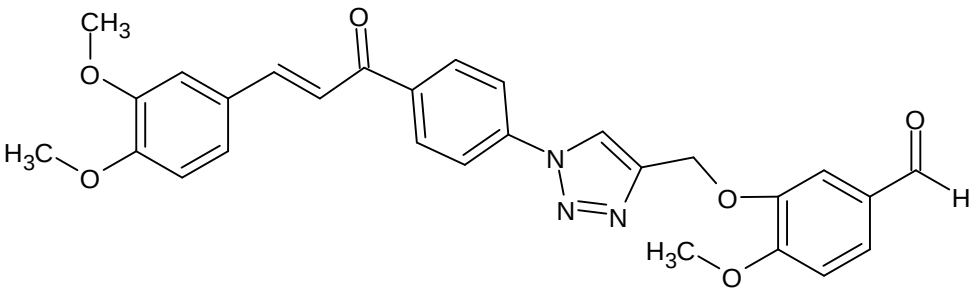
6c



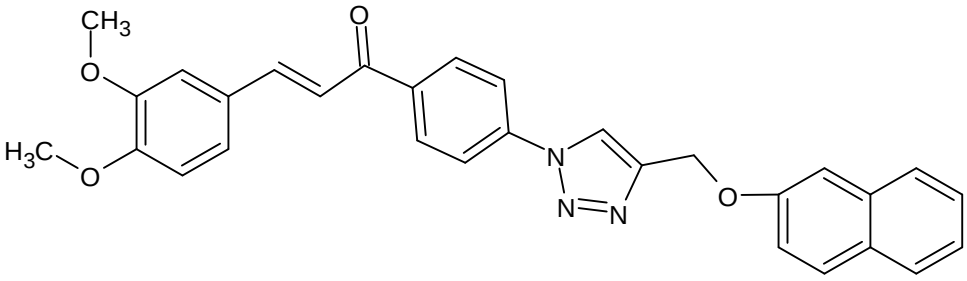
6d



6e



6f



6g

Ankita et al. synthesized a series of coumarin-triazole hybrids as potential multitargeted drug ligand with improved activity profiles. Studies proven that inhibitor of cholinesterase have significant role in Parkinson treatment. Ankita et al. synthesised coumarin -triazole hybrids with cholinesterase inhibitor activity. All synthesized coumarin-triazoles were screened for the cholinesterase inhibitory activity using Ellman and fluorescence resonance energy transfer (FRET)assay [43].

Dimitra Hadjipavlou-Litina et al. carried out synthesis of Novel 1,2,3-Triazole-Containing Nitrones and proved their antioxidant property.General Procedure for the Synthesis of (1,2,3-Triazole)Acetaldehyde Diethyl Acetals 10a–f derivatives is explained as to a solution of azide 11 (1 mmol) in ethanol (1 mL) and water (1 mL), CuSO4 × H2O (0.1 mmol) and sodium ascorbate (0.05 mmol) were added, and these were followed by the respective alkyne 12a–f (1 mmol). The suspension was microwave-irradiated in the Plazmatronika RM microwave reactor (30 W) at 40–45 ◦C for 1 h. After cooling, the solvent was removed in vacuo and the residue was suspended in chloroform (5 mL) and filtered through a layer of Celite. The obtained solution was concentrated in vacuo, and the crude product was chromatographed on a silica gel with a methylene chloride–methanol mixture (200:1, 100:1 and 50:1, v/v) to give the respective pure 1,2,3-triazole Acetaldehyde Diethyl Acetals [44].

Khatereh et al. synthesized 1,4 disubstituted 1,2,3 - triazoles by using ultraviolet assisted technique.The general process for making derivatives of triazoles by ultrasonic irradiation was applied to a combination of sodium azide(1.2 mmol),benzyl halide(1.0 mmol) and phenylacetylene derivative(1.2mmol)in water(3 ml).Thin layer chromatography was used to track the reactions development.After everything was finished , the solvent was eliminated and the was filtered out.An ehanol/water mixture was used to purify the final product [45].

Elise et al. carried out the synthesis of 1,2,3-traizole containing compounds. The general procedure for the synthesis explained as the alkyne (1.0 equiv.) was dissolved in THF:H2O(0.08M,1:1) in a round bottom flask that was charged with a stirbar. A mixture of sodium ascorbate (0.50 equiv.), copper sulphate pentahydrate (0.20 equiv.), and THF:H2O (0.08M,1:1:) was placed ina different flask. The azide (1.0equiv.) dissolved in THF (abut 2-3ml) was added to this mixture. The flask holding the alkyne was then filled with azide mixture all at once. Partitioning the ethyl acetate and washing with water and drying over anhydrous sodium sulfate, and concentration by rotary evapouration, usuallyflash chromatography was used to purify crude product [46].

CONCLUSION

The Triazole scaffold is evident to having potential therapeutic activity against parkinsonism disease. As per studies 1,2,3- triazole and 1,2,4- triazole have varying pharmacological activity like antioxidant, MAO inhibiting activity, Anticholinesterase, Neuroprotective activity. So these scaffold can be developed to treat parkinsonism. A review of triazole containing heterocyclic compounds having antiparkinsonism activity along with their structures and synthesis has been presented in this paper.

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