A DISSERTATION ON

Insights into the triad of neurotoxins, targets and associated disorders to identify possibly hazardous neurotoxic alert

SUBMITTED TO THE
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IN BIOINFORMATICS
BY

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M. Tech Bioinformatics (IV Semester)
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UNDER THE SUPERVISION OF

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DECLARATION FORM

I, **S Nailah Jawed**, a student of **M.Tech Bioinformatics** (II Year/ IV Semester), Integral University have completed my six months dissertation work entitled **"Insights into the triad of neurotoxins, targets and associated disorders to identify possibly hazardous neurotoxic alert"** successfully from **Council Of Scientific and Industrial Research - Indian Institute of Toxicology Research (CSIR-IITR)** under the able guidance of **Dr. Parthasarathi Ramakrishnan, Principal Scientist.**

I, hereby, affirm that the work has been done by me in all aspects. I have sincerely prepared this project report and the results reported in this study are genuine and authentic.

S. Nailah Jawed

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यह प्रमाणित किया जाता है कि **सुश्री एस नाईला जावेद** [Enrollment No: 1700101454] **M.Tech. (Bioinformatics)**, Integral University, Lucknow-226026, Uttar Pradesh में अध्ययन कर रही है । इन्होने विषय **"Insights into the Triad of Neurotoxins, Targets and Associated Disorders to Identify Possibly Hazardous Neurotoxic Alert"** विषय पर दिनांक **24/01/2023** से **25/07/2023** तक शोधकार्य का प्रशिक्षण **डॉ रामकृष्णन पार्थसारथी,** प्रधान वैज्ञानिक, सीएसआईआर-आईआईटीआर लखनऊ, उत्तर प्रदेश के पर्यवेक्षण में प्राप्त किया है इस कार्य या इसके किसी अंश को अधोहस्ताक्षरी के बिना लिखित अनुमति के प्रकाशित नहीं किया जाएगा।

हम सभी **सुश्री एस नाईला जावेद** के उज्जवल भविष्य की कामना करते है।

To Whomsoever It May Concern

This is to certify that **Ms. S Nailah Jawed** [Enrollment No: 1700101454] student of **M.Tech. (Bioinformatics)**, Integral University, Lucknow-226026, Uttar Pradesh has undergone short term dissertation training on **"Insights into the Triad of Neurotoxins, Targets and Associated Disorders to Identify Possibly Hazardous Neurotoxic Alert"** during **24/01/2023** to **25/07/2023** under **Dr. Ramakrishnan Parthasarathi,** Principal Scientist, CSIR - Indian Institute of Toxicology Research, Lucknow, Uttar Pradesh. The work should not be published, even in part without the prior written permission of the undersigned.

We wish **Ms. S Nailah Jawed** success in her future endeavours.

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I wish her good luck and bright future.

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I wish her good luck and bright future.

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S. Nailah Jawed

LIST OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVATIONS

BBB	Blood Brain Barrier
SMILES	Small Molecule Input Line Entry System
ADME	Absorption,Distribution,Metabolism,Excretion
GABA	Gamma-Aminobutyric Acid
NIOSH	The National Institute for Occupational Safety and Health
PIL	Python Imaging Library
ADHD	Attention deficit hyperactivity disorder
DDT	Dichlorodiphenyltrichloroethane
AM	Amiodarone
DEA	Desethylamiodarone
NMDA	N-methyl-D-aspartate
nAChRs	nicotinic Acetylcholine Receptors
AChE	Acetylcholinesterase
CYP450	Cytochrome P450
LC-MS	Liquid Chromatography-Mass Spectrometry
SSRI	Serotonin Reuptake Inhibitor
PNS	Peripheral Nervous System
TPSA	Topological polar surface area
PCA	Principal Component Analysis
ADT	AutoDock Tools
PIP	Preferred Installer Programme
CNS	Central Nervous System
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital

INTRODUCTION

The spinal cord and brain, which control bodily functions, make up the central nervous system. The skull protects the brain, separating it from the bloodstream by the blood-brain barrier (Alajangi *et al.*,2022). However, the brain is still susceptible to trauma, strokes, degenerative diseases, and infections (Bloom *et al.*,2006). Many psychiatric disorders, including schizophrenia and clinical depression, are thought to be linked to abnormalities in the brain (Fantegrossi *et al.*,2018). Through the use of selective transport mechanisms and tight junctions, the BBB keeps haemostasis processes in check (Schlosshauer *et al.*,1993). Excitatory neurotransmitters released in response to injury can cause deficits in neuronal function, such as memory loss, cognitive decline, and motor dysfunction. This can lead to cell death and neurological damage (Moretti *et al.*,2015). Neuronal apoptosis is the cause of many aging-related neurological disorders, such as Alzheimer's, Parkinson's, and stroke, due to a combination of genetic and environmental factors, as well as ageing itself. This is triggered by upstream effectors, mitochondrial changes, and caspase activation (Mattson *et al.*,2001).

The nervous system is divided into two parts: the central nervous system (CNS) and the peripheral nervous system (PNS). Astrocytes are essential for BBB development, neurotransmitter clearance, and neuron support. Acetylcholine, norepinephrine, glutamate, gamma-aminobutyric acid (GABA), and dopamine are some examples of neurotransmitters. Being common in the general population, nervous system disorders contribute up to 11% of the global burden of disease. 10% to 20% of children are thought to have developmental disabilities, Environmental factors such as exposure to the environment and genetic susceptibility are responsible for 25% of these disabilities (Sousa *et al.*,2017). Mental, neurological, and substance use disorders were the leading cause of global YLDs (years lived with disability) in 2010, with 56.7% caused by mental disorders, 28.6% by neurological disorders, and 14.7% by substance use disorders (Whiteford *et al.*,2015). Neuronal death can occur through cellular and molecular mechanisms, such as oxidative stress, calcium overload, mitochondrial toxicity, changes in cell energetics, or disruption of the cytoskeleton (Jokanović *et al.*,2011).Because it denotes the death of neurons, "neuropathy" is thought to be the most severe form of neurotoxicity (Costa *et al.*,2008).

The axon is the main target of neurotoxicity, with the distal portion of the axon being the first to be affected, leading to a chemical transection and degeneration. Toxins may target astrocytes as a target, and astrocytes can contribute to neurotoxicity (Moser *et al.*,2008). In addition to affecting cognitive function, memory, and communication, even minor injuries can have a negative impact on other skills including alertness and attention. Neurotoxicity can occur at any stage in the life cycle from development to maturity, and its symptoms may

change as people age. Severe form of injuries like mortality, convulsions, impaired coordination, a coma, paralysis can result due to these toxicants exposure which may lower the quality of life.

Neurotoxicity is the ability of chemical, biological, or physical agents to adversely affect the nervous system's functionality or structural makeup. Neurodegenerative diseases are a growing concern worldwide, and their impact on individuals, families, and society is significant (Bertram *et al.*,2005). Therefore, it is crucial to invest in research and development of treatments for neurodegenerative diseases to improve the quality of life for those affected and reduces the burden on healthcare systems. Additionally, promoting awareness and prevention measures can help mitigate the risk factors associated with neurotoxicity (Marras *et al.*,2019).There are no known cures for neurodegenerative diseases, but some symptomatic ones have been found to slow the disease's progression (Sarne *et al.*,2005). Examples of symptomatic treatments for neurodegenerative diseases include drugs that improve cognitive function in Alzheimer's disease and Parkinson's disease, as well as drugs that raise dopamine levels (Duraes *et al.*,2018).

Chemical toxins may have a variety of different impacts on the neurological system.When the normal function of the nervous system is affected by exposure to hazardous chemicals (neurotoxicants), either naturally occurring or created by humans, neurotoxicity occurs. According to clinical reports, epidemiological research, and experimental studies, at least 25 substances can produce neurobehavioral symptoms in people or animals (Costa and L. G, et al 2017).Neurotoxicity is cited as a basis for establishing limits on occupational exposure in 36 (40%) of the 91 criteria papers produced by NIOSH (Anger and W. K. *et al.*,1989).

A very low number of compounds have been tested for toxicity purpose and evaluating them for neurotoxicity is to be accelerated. Thus, determining how many industrial and commercial chemicals are neurotoxic is difficult (Grandjean *et al.*,2006). Yet, there is evidence that a wide range of hazardous compounds in common usage have the potential to be neurotoxic (Hatcher *et al.*,2008). Chemotherapy can cause both central and peripheral neurotoxicity, with myopathy and CIPN being the main side effects (Taillibert *et al.*,2016). Lead has also been reported to have direct neurotoxic effects on astroglia and oligodendroglia (Lidsky *et al.*,2003).The term "mild cognitive impairment" refers to a syndrome of cognitive decline that is greater than would be expected for a person's age and level of education, but does not significantly affect day-to-day functioning. It can be treated as a secondary preventive measure because it is a risk factor for dementia (Gauthier *et al.*, 2006).Studies have shown abnormalities in mood swings, and it is important to study pathologies like bipolar disorder to better understand how the cerebellum and mood changes are related (Lupo *et al.*,2019). Alzheimer's dementia affects 30 million people worldwide, and the World Health Organization predicts that over the next 20 years, that number will triple. Alzheimer dementia is a very common disease, with the cumulative incidence estimated to increase from about 5% by age 70 to 50% by age 9(Jahn *et al.*, 2022).

There are currently very few webservers or online prediction tools available to identify the neurotoxic compounds which may be present in pharmaceutical or industrial products. Numerous medications used to treat various diseases weaken the neurobiological system. Altogether, a neuroprotective strategy has yet to be recommended for prevention and treatment of neurotoxicity. We included a literature-based study in order to gather data on the topic. We compiled a list of neurotoxic compounds and performed a physicochemical analysis to identify descriptors such as molecular weight, hydrogen bond donor, hydrogen bond acceptor, topological polar surface area, and rotatable bonds. To reduce dimensionality of large dataset, a chemical space analysis was performed using the PCA method to reduce dimensionality.3-D Graphs were generated using Data Warrior in order to analyze structure-activity data. A structural theory for how the neurotoxins modify their targets was developed using molecular interaction studies, and the neurotoxins were also classified according to their specific targets.The current in silico study hence, deciphers a precautionary measure to tackle the research gap between underlying neurotoxicity of products and prediction or identification of the neurotoxic structural alert. By gathering neurotoxins from different published investigations, using physicochemical descriptor calculations to determine the features affecting compound structure as well as function, identifying the principal component affecting their properties, and finally unravelling the structures to identify one structural motif common to them all by cross-checking the substructures with python programming modules such as RDkit, Pandas and PIL coupled with density functional theory in order to validate the results, we were able to create an in-depth understanding of the various neurotoxins. Our analysis suggests that these neurotoxins can have significant negative effects on both the environment and human health, highlighting the need for further research and regulation to mitigate their impact. This early diagnosis can lower the risk of drug-induced brain injury and aid in the development of safer medications. To improve patient outcomes and save healthcare costs, neurotoxic chemicals must be identified and eliminated throughout the therapeutic development process.

AIMS AND OBJECTIVES

The focus of my study was on gaining insights into the molecular interaction of toxins involved in neurological disorders and finding toxic moieties amongst the many chemicals used in the health, pharma and other industries. We proposed the following objectives with the aim to detect possibly hazardous neurotoxic alerts by gathering insights into the trinity of neurotoxins, targets, and related conditions.

- Collection of toxins correlated to several distinct neurological disorders and the identification of their physicochemical characteristics and principal component analysis.
- Determining the structural alerting that is possibly triggering neurotoxicity.
- Research using molecular docking to unravel the underlying chemistry of the toxin-target relationship and the evaluation of global reactivity parameters as a toxicity indicator.

REVIEW OF LITERATURE

As a consequence of advances in diagnosis and treatment, there has been a rise in the neurotoxicity cases worldwide. Neurotoxicity can be caused by various factors such as exposure to chemicals, drugs, and radiation. It is important to continue researching and developing new treatments to prevent and manage neurotoxicity. Environmental chemists have come under increasing public and societal pressure over the recent past to detect dangerous chemicals and substitute them with "eco - friendly alternatives," or safer, alternatives while shunning animal testing of every chemical, which is also unviable from an economic and innovative perspective. Animal models have also come under heavy fire for being immoral, prohibitively costly, and untrustworthy for projecting outcomes and conclusions to people (Alves *et al.*,2016).

Structure-based alerts, often referred to as toxicophores or toxic fragments, may be a sign that a substance may have the potential to negatively impact a particular organ in a particular way. Often employed in environmental toxicology and medication development, they provide a simple technique for detecting potentially dangerous compounds. Computational models have proven to be reliable, rapid, and cost-effective choices for the toxicity assessment of chemicals in the early phases of drug discovery or environmental safety review. In fingerprint-based approaches, precisely defined fingerprints of various lengths are the source of substructures. Industries can use recognized structural clues to predict a chemical's potential threat for certain side effects. For instance, a structural warning can be promptly employed as a high-risk indicator. Frameworks for structural-alert-based pharmacological design and implementation are quite beneficial in terms of comprehension and visualization. Lately, significant advancements have been made in the recognition and application of structural warnings in toxicology (Yang H *et al.*,2020).

By quickly hydrolyzing the neurotransmitter acetylcholine in a variety of cholinergic pathways in the central and peripheral nervous systems, acetylcholinesterase participates in the termination of impulse transmission. Organophosphate-related intoxication is treated pharmaceutically by administering oxime reactivators of the inhibited enzyme activity as causal drugs after the poisoning. However, the effectiveness of oxime reactivators decreases with time and depends on the severity of the poisoning (Colovic *et al.*,2013).

Amphetamine has a high potential for abuse and can be neurotoxic. They are now being prescribed for adults with ADHD (Attention deficit hyperactivity disorder) and narcolepsy as maintenance therapy,

extending the potential exposure time. It is crucial to reevaluate the likelihood of negative effects from adult patients receiving chronic treatment. Amphetamine prescription use can result in negative psychological effects like stimulant-induced psychosis. Identification of biochemical factors that increase risk and decrease protection, as well as assessments of central toxicity and detrimental psychological effects during late adulthood and senescence, is required (Berman *et al.*,2009).

DDT (Dichlorodiphenyltrichloroethane) and dieldrin are the main chemicals in organochlorine insecticides, and the production of tremors or convulsions is the main sign of their neurotoxicity. The effects of DDT are thought to be due to effects on neuronal membranes. DDT and dieldrin alter levels of neurotransmitters, including acetylcholine, serotonin, norepinephrine, and dopamine, in different ways (Shavali *et al.*,2004).

Studies have shown that AM (Amiodarone) and DEA (desethylamiodarone) both raiseintrasynaptosomal [Ca 2 +] by acting on NMDA receptors. This is caused by increased influx through the receptor-mediated channel and not by release from intracellular storage sites. Thisdisruption in cellular biochemical homeostasis may cause cell injury, and cell viability isthreatened when Ca 2 + homeostasis fails .Tremor, ataxia, and peripheral neuropathy have all been described as neurotoxic effects of Amiodarone. Parkinsonism has also been reported as one of the basal ganglia dysfunction symptoms that have been linked to Amiodarone.The buildup of Amiodarone in the brain maycontribute to the neurotoxicity that causes Parkinsonism (Kodavanti *et al.*,1992). Strychnine is one of the major biologically active and toxic constituents of Nux. In the study, theneurotoxic effects of strychnine and the contribution of individual metabolic differences to susceptibility to strychnine neurotoxicity were investigated. The results showed that the striatum and cortex are the main targets of strychnine toxicity and that CYP3A1 could be a sensitive biomarkerof strychnine neurotoxicity. These results provide valuable information on the neurotoxic sensitivity of strychnine, which will facilitate the rational clinical use of strychnine, possibly includingstrychnine(Ishida *et al.*,2010).

The hippocampus is a center of learning and memory, receiving abundant cholinergic innervations and expressing abundant nicotinic acetylcholine receptors (nAChRs). The mechanisms of nicotine acting on the hippocampus affect attention, learning and memory. The nAChRs and the cholinergic innervation of the hippocampus are reduced in Alzheimer's dementia. Using mouse hippocampal regions, we investigated the potential diversity of nAChR effects on collateral Schaffer synapses in CA1 pyramidal neurons. When nAChR currents are locally evoked at these excitatory synapses, various outcomes can occur depending on the relationship between nAChR(Jiang *et al.*,2022).Cannabinoid receptors, CB1 and CB2, are G protein coupled receptors that regulate signaltransduction pathways such as adenylyl cyclase

inhibition, mitogen-activated protein kinaseactivation, calcium and potassium channel regulation, and other signal transduction pathways.There have been discoveries of cannabinoid receptors in the sensory, autonomic, and central nervous systems. In the central nervous system, they are found in the cerebral cortex, hippocampus, basal ganglia, and cerebellum, where they are highly abundant, sparse in the brainstem, and less abundant in the hypothalamus and spinal cord.The development of novel agonist ligands with pharmacologically selective properties may result from the existence of receptors(Ge S *et al.*,2005).

Toluene is widely used as a cleaning and drying agent in the rubber and lumber industries, as well as in the dry cleaning, motor, aviation, and chemical industries. Toluene is a solvent that is produced in large quantities each year—more than 3 million tons—not only in the United States but also in many other industrial and household products.These inhalants pose a particular riskto children due to their availability, ease of use, legality, and cheapness. Studies have revealed both acute and long-term effects of toluene, with the CNS being its primary target. Chronicencephalopathy linked to long-term toluene abuse is particularly significant, with symptoms suchas memory loss, difficulty concentrating, and impaired coordination persisting even after theindividual stops using toluene(Sarne Y *et al.*,2005).

Cannabinoid receptors 1 (CB1R) and 2 are two members of the G-protein coupled receptor family that play a role in the biological effects of cannabinoids, the primary chemical components of the ancient medicinal plant Cannabis sativa (marijuana), on the body. The CB1R is the dominant subtype in the CNS and has received a lot of attention as a potential therapeutic route in a number of pathological conditions, including neuropsychological disorders and neurodegenerative diseases. Cannabinoids also modifysignal transduction pathways and have a significant impact at peripheral sites (Filley *et al.*,2004).

Cannabinoid neurotoxic effects have been attributed to several mechanisms, including caspase activation, ceramide buildup, and stimulation of different MAPK pathways. Calcium ions play a significant role in spreading the damage to new brain areas because NMDA receptors encourage calcium entry into nearby cells. In the same way, it is anticipated that cannabis will cause neurotoxicity rather than neuroprotection if they amplify calcium entry and increase intracellular calcium ion concentration (Zou *et al.*, 2018).

GABA(Gamma-aminobutyric) is the main mediator of inhibitory transmission in the mammalian central nervous system. It interacts with other neurotransmitter systems and functions via ionotropic A and metabotropic B type receptors. GABA-A receptors are ligand-gated ion channels composed of five subunits from eight families. The most prevalent GABA-A receptor composition is 2a, 2b, 1g, such as a1b2g2 or a2b3g2. GABA binding opens up a Cl channel, and positive modulators such as barbiturates,

benzodiazepines, steroids, and ethanol have binding sites on GABA-A receptors. GABA-B receptors consist of two B1 and B2 subunits, each with seven transmembrane segments. The extracellular N-terminus of the B1 subunit binds ligands, while the B2 subunit is responsible for receptor trafficking and its interaction with the cognate G-protein. Gamma-aminobutyric (GABA) system dysfunction in the brain has long been linked to anxiety spectrum disorders. Chronic stress has been shown to activate GABAergic forebrain regions, such as the hippocampus and dorsomedial hypothalamus. Studies have shown that depressed people have significantly smaller hippocampus. Therefore, targeting the GABAergic system may provide a potential therapeutic approach for anxiety and mood disorders by regulating the activity of these regions and promoting neurogenesis in the hippocampus. However, further research is needed to fully understand the role of the GABAergic system in these disorders and to develop effective treatments (Zhou and J.,2004).

Acetylcholinesterase is found at the junction of muscle and nerve cells, in the postsynapticneuromuscular junction. It breaks down acetylcholine into acetic acid and choline, which bindsto cholinergic receptors and activates them, causing muscles to contract. It is present in theneuromuscular junction to facilitate movement. Exogenous purified AChE induced the growth ofneurites from chick nerve cells, and a peripheral site inhibitor prevented neuritogenesis. It alsoencourages the formation of amyloid fibres and has a synaptogenic function in microinjectedXenopus tadpoles. Purified recombinant AChE increased dopamine release from midbraindopamineneurons.These findings suggest that AChE plays a crucial role in neuronal development and function, as well as in the regulation of neurotransmitter release. Further research on the mechanisms underlying these effects could have implications for the treatment of neurodegenerative diseases and psychiatric disorders (Howlett *et al.*,2022).

On a variety of catecholamine-responsive target cells, the initial recognition sites are alpha1 and alpha2-adrenergic receptors. The structural similarities between alpha-adrenergic receptors and other types of membrane receptors connected to guanine nucleotide-binding regulatory (G) proteins include seven membrane-spanning domains with extracellular amino termini and intracellular carboxyl termini. These G proteins seem to connect alpha-adrenergic receptors to a variety of effector systems, such as ion channels and enzymes like adenylate cyclase and phospholipases (Nichols *et al.*,2008).

Glutamate plays a key role in brain function through receptor proteins found on pre- and post-synaptic neurons, divided into ionotropic (iGluRs) and metabotropic (mGluRs). iGluRs areresponsible for the mammalian CNS's quick excitatory transmission. iGluRs transmit signals into postsynaptic neurons on a millisecond timescale, producing a synaptic current that controlsmemory and learning. N-methyl-d-aspartate (NMDA),amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors

areadditional subtypes of iGluRs. mGluRs mediate slow glutamate responses, producing synapticactivity changes that last for a long time. The control of excitatory synaptic transmission issignificantly influenced by NMDA receptors. For an NMDA receptor to be activated, ligandsmust occupy both the glutamate site and the cofactor glycine site (Kalueff *et al.*,2007).

Carbonic anhydrases are zinc enzymes present in prokaryotes and eukaryotes, encoded by fourdistinct gene families: alpha-CAs, beta-CAs, gamma-CAs, and delta-CAs. They are present invertebrates, Bacteria, algae, chloroplasts, Archaea, and marine diatoms.Basically, there are four membrane-bound isozymes (CA IV, CA IX, CA XII, and CA XIV), four cytosolic forms (CA I–III, CA VII), one mitochondrial form (CA V), and a secreted CA isozyme (CA VI). These enzymes are involved in vital physiological processes such as respiration and transport of CO2/bicarbonate between metabolising tissues and lungs, pH and CO2 homeostasis, electrolyte secretion in a variety of tissues/organs, biosynthetic reactions (such as gluconeogenesis, lipogenesis, and ureagenesis), bone resorption, calcification, and many others (Soreq H and Seidman S .,2001).

CYPs are important enzymes that regulate neurotransmitters, steroids, and cholesterolhomeostasis. Recent research has shown that psychiatric and neurodegenerative disorders may beinfluenced by these enzymes. To better understand their role in healthy brain physiology, disease,and localization, characterization of brain CYP isoforms, substrates, and metabolic end-productsis needed. Additionally, research into how dietary choices and toxicity exposure affect brain CYPactivity is needed.They play an important role in bioactivating drugs and causing cellular damage in the target blood brain barrier. The blood-brain barrier is a selective barrier that protects the brain from harmful substances, and CYPs can disrupt this barrier leading to various neurological disorders. Therefore, understanding the role of CYPs in the blood-brain barrier is crucial for developing effective therapies for these disorders (Insel and P. A.,1989).

Cytochrome P450 (CYP) enzymes are metabolized by the liver and extra-hepatic tissues,including the brain. Brain CYPs are concentrated close to drug targets and have the potential toaffect local metabolism. Individual variations in brain CYP metabolism can affect sensitivity andresponse to medications, behaviour, susceptibility to diseases, and the effectiveness oftreatments. Drug-metabolizing CYPs are distributed in the brain in a heterogeneous manner.Transcriptional, posttranscriptional, and post-translational mechanisms control brain CYPs. Studies conducted in vitro imply that CYP2D6 may contribute to the biosynthesis of crucial brain signalling molecules like dopamine and 5-hydroxytryptamine. Due to the high polymorphism of the CYP2D6 gene, there is a wide variation in CYP2D6 activity between individuals.Poor metabolizers of CYP2D6 are linked to increased anxiety and

impulsivity due to higherthalamic cerebral activity(Jeon *et al.*,2010).

Another study examined the effects of strychnine on the nervous system and how individualdifferences in metabolism affect a person's susceptibility to its neurotoxic effects. A single doseof strychnine (2.92 mg/kg) was used to study the acute toxicity in rats, and the rats' stages ofepilepsy were graded using Racine's scale. High performance liquid chromatography tandemmass spectrometry (LC-MS/MS) was used to measure the levels of strychnine in the cortex,striatum, hippocampus, and plasma tissues. The concentration of strychnine in rat plasma, liver,and brain changed significantly with changes in Cyp3a1 expression levels. The concentration ofstrychnine in the STR group was higher in the liver than in plasma and brain, suggesting that theliver is where strychnine is metabolized. The protein CYP3A1 can be used as a susceptibilitymarker for strychnine-induced neurotoxicity(Jiang *et al.*,2022).

G-protein-coupled receptors called muscarinic M1–M5 acetylcholine receptors control numerouscrucial processes in the central and peripheral nervous systems. Given their high conservation ofthe acetylcholine-binding pocket, the M1 and M4 receptor subtypes in particular have emergedas promising drug targets for the treatment of neurological disorders like Alzheimer's disease andschizophrenia. M1 and M4 receptors are highly expressed in the brain regions that are affected inAlzheimer's disease and schizophrenia. Therefore, targeting these receptors with specific drugscould potentially alleviate symptoms associated with these disorders (Jahn H., 2022).

Out of 217 patients with neurological complications, 28% experienced seizures,including convulsive, non-convulsive, focal, generalized, or initially focal with secondarygeneralization. Seizures can occur without obvious tonic-clonic movements. Seizurescan occur in critically ill patients taking muscle relaxants, but may not cause motoreffects. Systemic causes include epilepsy and underlying neurological disease (Delanty *et al.*,1998).Arsenic-contaminated water and agricultural products have led to increased illnessesand fatalities worldwide, primarily affecting cancer and skin conditions. Lead poisoningincreased due to industrialization, forcing governments to reduce usage. Mercury, aharmful nutrient, is particularly harmful to lactating women, foetuses, and children.Admitium, a carcinogenic element, poses a significant risk to humans, both in occupational and non-occupational settings(Achparaki *et al.*,2012).

Serotonin syndrome is a life-threatening condition linked to serotonin reuptake inhibitor(SSRI) drugs, which can cause tremor and akathisia. SSRIs can cause tardivedyskinesia, but rarely without a history or current use of neuroleptics. Lithium andvalproic acid can cause parkinsonism and tremors. Myoclonus and asterixis can occurat therapeutic doses of certain medications, but are typically caused by toxic doses

ofother medications. Non-toxic doses of medications rarely cause ataxia(Friedman and J. H.,2020).

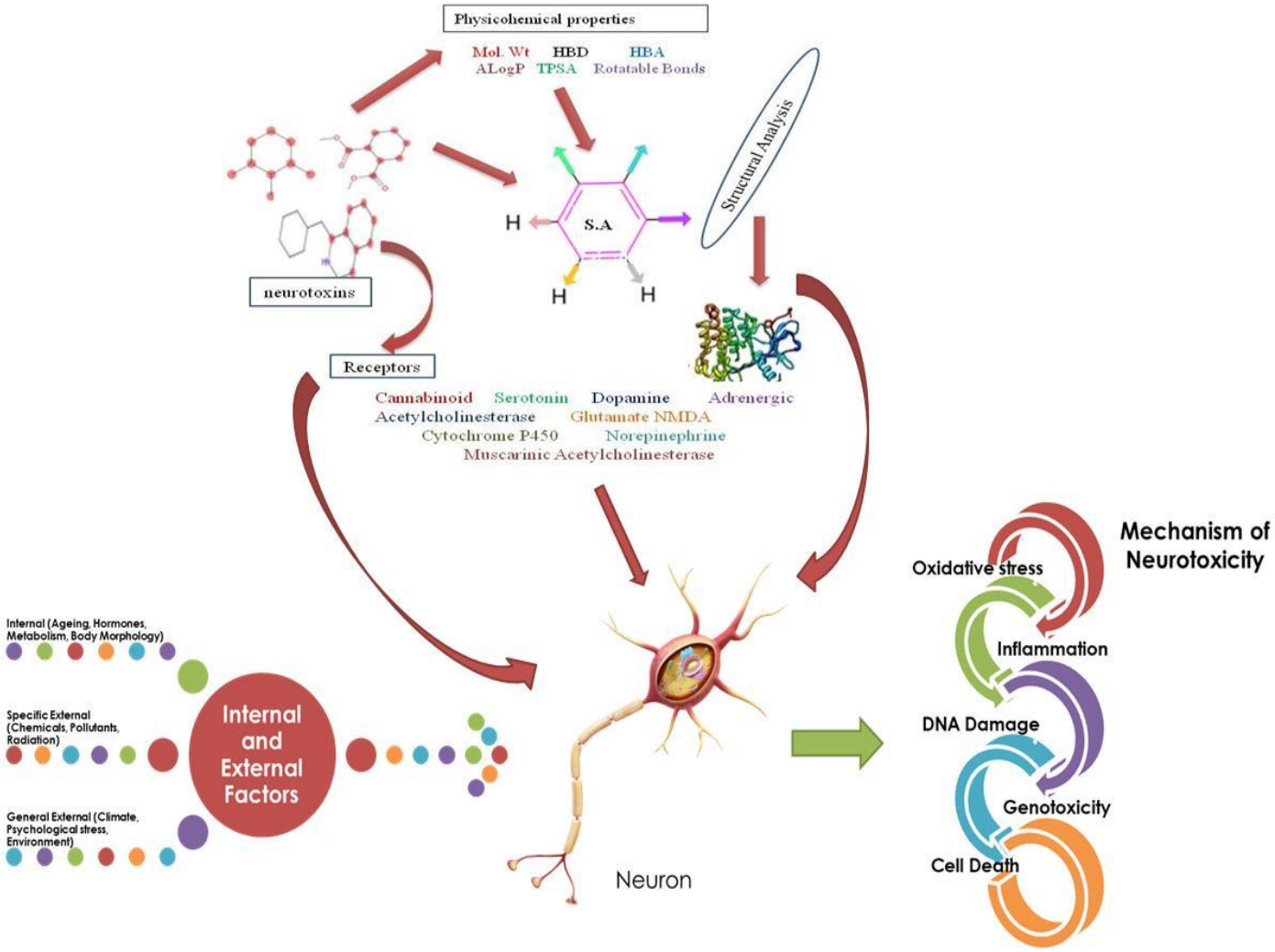


Figure 1. Showing Mechanism of Neurotoxicity

MATERIAL & METHODS

Software and Tools Used for Analysis

Swiss Target Predictor

For any bioactive small molecule, SwissTargetPrediction is a web-based tool that has been available since 2014. It performs ligand-based target prediction. Non-experts are protected from methodological pitfalls and experts from tiresome technical tasks by the user-friendly graphical interface. To weight 2D and 3D similarity parameters in a so-called Combined-Score, the SwissTargetPredictionmodel was trained by fitting a multiple logistic regression on various size-related subsets of known actives. The likelihood that the molecules will share a common protein target is predicted by a combined-score greater than 0.5. The Combined-Score in reverse screening enables one to determine the likelihood that a given query molecule will target a specific protein, presuming that the molecule is bioactive.SwissTargetPredictionmeasures how similar the user's query compounds are to those assembled in curated collections of known actives in binding assays.SwissTargetPrediction2019 is a major update with updated bioactivity data, a re-trained model, a more efficient backend, and novelties in the web interface. The reverse screening engine now yields predictions among more possible protein targets, but the process is faster and the high predictive performance level is maintained (Daina *et al.*,2019).

To find the macromolecular targets of our collections of neurotoxins, the webserver used was Swiss target prediction. The molecular sketcher on the right lets you draw or import any molecular structure, or you can write or paste SMILES in the input text box on the input page to submit a query molecule. The text box's content and the sketchers are in sync. The option to load examples is available. Additionally, you can decide which types of protein targets will be used for the prediction.The link http://www.swisstargetprediction.ch/index.php may be used to access the same.

Therapeutic Target Database

This database contains details on the known and explored therapeutic protein and nucleic acid targets, the targeted disease, information on the relevant pathways, and the drugs that are specific to each of these targets.Drug discovery requires knowledge of comparative agents and targets, prodrugs, co-targets, off-target investigations, collective structure-activity and drug-likeness landscapes, and poor binders and non-binders for developing discovery tools. Molecular docking is a structure-based approach to drug discovery that rates how well molecules bind to a target site using scoring functions. Tools for screening bioactive molecules and pharmaceutical properties have been developed using AI techniques, and they have primarily been trained by actives (binders)

and non-actives (poor binders, non-binders). It is crucial to have easy access to therapeutic target weak binders and non-binders. Identifying weak binders and non-binders can help researchers understand the characteristics of molecules that are not suitable for drug development, which can save time and resources. Additionally, studying these molecules can provide insights into the underlying mechanisms of drug-target interactions. Drug discovery has advanced rapidly, leading to the collection of vast amounts of data in TTD and other databases, which can be used to enhance drug discovery and create drug identification tools. This update includes 159 and 1658 newly emerged targets and drugs, a multi-entry target search function, 534 prodrug-drug pairs, 1127 co-targets, 427 262 active agents, 33 598 drug-like properties, and cross-links to target structure in PDB and Alpha Fold(Zhou *et al.*,2022).

The database proved to be a valuable resource for our research, providing us with a comprehensive understanding of the targets, diseases, and drugs associated with our study. With this information, we were able to make informed decisions about our research methodology and draw meaningful conclusions from our findings.The link https://idrblab.org/ttd/may be used to access the same.

SchrödingerCanvas

Using SchrödingerCanvas 2.9, the physicochemical properties were computed (Duan J *et al.*,2010).A variety of applications for structural and data analysis are offered by the cheminformatics program Canvas, including fingerprinting, similarity searching, substructure searching, selection by diversity, grouping, and creating regression and classification models.Calculations were made for the following descriptors: Molecular Weight, ALogP, Hydrogen Bond Donor, Hydrogen Bond Acceptor, Rotatable Bonds, Polar Surface Area, Ring Count, and Heavy Atom Count. Descriptors were finally saved in Excel for later analysis .

R Studio

The integrated development environment for R, a language for statistical computation and graphics, is called RStudio. There are two versions offered: While RStudio Server operates on a remote server and enables access to RStudio via a web browser, RStudio Desktop is a standard desktop program. The desktop version can be downloaded from http://www.Rstudio.com .The goal of principal component analysis is to visualize and summarize multivariate data. Unlike the other methods, PCA only functions with quantitative variables. There are many uses for principal component analysis in daily life, including finance, image processing, healthcare, and security. It has many uses in the design of pharmaceuticals as well.

Through R Studio, we can create various PCA plots, including Biplot, Screeplot, and Boxplot. PCA can help identify key variables that contribute to the variation in data, making it a valuable tool for decision-making in

various industries. Additionally, PCA can be used to reduce the dimensionality of large datasets, making it easier to analyze and interpret complex information (RStudio.T.,2020).

Autodock Vina

Dr. Oleg Trott, of The Scripps Research Institute's Molecular Graphics Lab (now CCSB), is the creator and implementer of Autodock Vina. Autodock Vina is currently at version 1.2.0. . Vina utilizes the same PDBQT molecular structure file format as AutoDock for input and output. MGLTools can be used to create (interactively or in batch mode) and view PDBQT files. There is no need for additional files like the grid map files or the AutoDock and Auto Grid parameter files (GPF, DPF).Vina's design ethos avoids requiring the user to comprehend its implementation details, tweak esoteric search parameters, cluster results, or be knowledgeable in advanced algebra (quaternions). The structures of the molecules being docked and the description of the search space, including the binding site, are all that are needed. It is not necessary to compute grid maps or assign atom charges. Vina is faster and more efficient than AutoDock 4, and can run on multiple CPUs or cores to reduce the time it takes to run. Vina now allows multiple ligands to be docked simultaneously, potentially useful in fragment-based drug design. AutoDock Vina 1.2.0 offers Python bindings and batch processing to speed up high-throughput virtual screenings. It also features simultaneous multiple-ligand docking against a single target structure, which can be accessed from either the command line interface or Python (Eberhardt *et al.*,2021).

Molecular docking is used to predict noncovalent binding of macromolecules and ligands, using unbound and MD simulations, homology modelling, etc. to predict the bound conformations and binding affinity. Docking is used to screen virtual libraries of drug-like molecules to find potential leads for drug development. It requires a large number of computational resources, so it is important to increase precision while reducing the time it takes. Additionally, Vina calculates its own grid maps quickly and automatically and does not store them on the disc, eliminating the need for manually selecting the atom types for grid maps, creating grid map files with AutoGrid, selecting the "search parameters," and clustering the outcomes after docking. Without revealing any intermediate information to the user, it also clusters and ranks the results (Trott, O and Olson, A. J.,2010).

https://github.com/ccsb-scripps/AutoDock-Vina

Discovery Studio

The Discovery Studio Visualizer Client is a graphical interface for accessing Discovery Studio Science. For managers and researchers who need to work with modellers but do not require access to the expert-level analysis tools in Discovery Studio, this free, user-friendly visualisation tool is the perfect solution. The Perl-based scripting API offers a wide range of common tasks and commands that make it possible to automate and

customise typical modelling tasks. View and share data on proteins and small molecules in a variety of formats that are compliant with industry standards (Studio, D.,2008).It provides unmatched capabilities for sharing data, workflows, and computational resources. It also provides scriptable actions such as molecular overlay, chirality and valency checks, secondary structure prediction, access to electrostatics tools, management of constraints/restraints, and surface diffraction. The open operating system SciTegic Pipeline PilotScitegic Enterprise Server platformTM, on which Discovery Studio is based, enables the seamless integration of third-party applications as well as protein modelling, pharmacophore analysis, and structure-based design.

Data Warrior

DataWarrior combines chemical intelligence with dynamic graphical views and interactive row filtering to display trends in multiple scaffolds or compound substitution patterns. Chemical descriptors store information about different facets of chemical structures, allowing for different molecular similarity measures.Scatter plots, box plots, bar charts, and pie charts show trends in multiple scaffolds or compound substitution patterns. OSIRIS is an adaptable, scalable, modular, and consistent software and database platform designed to support drug discovery data analysis. Calculations of physicochemical properties, the creation of structure-activity relationship tables, and the visualisation of activity cliffs are all possible. You can download DataWarrior installers from the download page (https://openmolecules.org/datawarrior/download.html) for Windows, Macintosh, and Linux. Both academic and commercial use of DataWarrior is free (Sander *et al.*,2015).

Castp

Computed Atlas of Surface Topography of Proteins (CASTp) is a web server that offers online tools for finding, defining, and quantifying geometrical and topological characteristics of protein structures. On a protein surface, pockets are void concavities that allow solvent (probe sphere 1.4 A) access; in other words, these concavities have mouth openings connecting their interior with the surrounding bulk solution. CASTp is a computational geometry algorithm that accurately defines the boundaries between the bulk solvent and pockets, identifies pockets and cavities analytically, and is rotationally invariant.CASTp 3.0 offers improved identifications and quantifications of protein topography, imprints of negative volumes of pockets, cavities, and channels, topographic features of biological assemblies in the Protein Data Bank, and enhanced protein visualization (Tian *et al.*, 2018).

You can freely access the CASTp 3.0 web server at http://sts.bioe.uic.edu/castp/.

RCSB PDB

By providing access to and tools for exploration, visualisation, and analysis of: experimentally determined 3D structures from the Protein Data Bank (PDB) archive Computed structure models (CSM) from Alpha Fold DB and Model Archive, RCSB Protein Data Bank (RCSB PDB) enables breakthroughs in science and education. This data can be investigated in light of outside annotations, which offers a structural perspective on biology. The Protein Data Bank (PDB) is a vital resource for research and education in fundamental biology, health, energy, and biotechnology. RCSB PDB is the US data centre for the PDB archive and is the first open access digital data source in biology and medicine. PDB offers access to 3D structure information for the molecules of life through an online information portal and a downloadable data archive. Protein structure prediction is becoming increasingly important due to the abundance of 3D structure data stored in the PDB, which has enabled breakthroughs in protein architecture. AI and deep learning techniques have been used to accelerate the process (Berman *et al.,* 2000). These methods have been shown to significantly reduce the time and resources required for protein structure prediction, making it possible to analyze large datasets and identify potential drug targets more efficiently. Additionally, the use of AI and deep learning has led to the discovery of novel protein folds and functions that were previously unknown. You can access the RCSB PDB at http://www.rcsb.org/.

SWISS ADME

The process of discovering new drugs involves analysing a large number of molecular structures to determine which ones have the best potential to treat patients. The fate of a therapeutic substance in the body is determined by its pharmacokinetics, and the ADME parameters (Absorption, Distribution, Metabolism, and Excretion) can each be assessed separately using specialised techniques. The percentage of pharmacokinetics-related failure in the clinical phases is decreased by early ADME estimation in the discovery phase. For the purpose of predicting ADME, computer models have been promoted as a viable alternative to experimental methods. Substructure searches and physicochemical parameters are used to remove chemicals from chemical libraries that are likely to be unstable, reactive, toxic, or interfere with biological assays. Cheminformaticians have developed molecular descriptors such as the molecular fingerprint (FP) and the FP2 method, which are used in classification models for ADME behaviours. CADD is a pioneer field for the application of machine learning technologies. SwissADME is a free web tool designed for easy submission and analysis of CADD results. It features advanced techniques and state-of-the-art tools, as well as various input methods, computation for multiple molecules, and the ability to display results (A.Daina *et al.,*2017). It is freely available at http://www.swissadme.ch.

Collection of neurotoxins

Structural information about the neurotoxins were retrieved from literature survey. The structures of one sixty-four major compounds were downloaded from Pubchem and CHEBL. A dataset of neurotoxins along with their

PubChem ID, compound name, and canonical SMILES was prepared. These structures were used in the molecular docking studies.

Physicochemical descriptor calculation

Various descriptors like Molecular weight, Hydrogen bond donor, Hydrogen Bond Acceptor, Topological polar surface area (TPSA), Rotatable bonds were calculated using Canvas Schrodinger platform. Physical and chemical characteristics play a significant role in a compound's pharmacokinetic profiling. After that Principal component analysis of the dataset was done using R Studio for dimensionality reduction.

Clustering of Neurotoxins

The neurotoxins were grouped together according to their individual targets using Swiss Target Prediction and a sanky diagram is drawn to display relationship among the neurotoxins, class, target and disease. The factors to keep in a PCA are determined using the Scree plot

Receptor Preparation

The three-dimensional structures of protein receptors, Acetylcholinesterase, Androgen, cannabinoid, serotonin, muscarinic acetylcholinesterase, cytochrome P450, Alpha-2a Adrenergic,CarbonicAnhydrase,Glutamate, Dopamine and GABA receptor were retrieved from the Protein Data Bank (PDB) using PDB IDs:1VZJ.1E3G, 6KPF,6VRH,6WJC,2HI4,6KUX,1A42,2ZNT,2QMZ and 7QN5, respectively.To avoid steric clashes, the structure was pre-processed before docking by removing the HETATMs, which include water ions, small molecules, and other residues. All the pre-processing is achieved by using Discovery Studio. To obtain the final structure of the biological target proteins, Kollman charges were applied to the modified structure, polar hydrogens were added to the macromoleculesand then solvated using the AutoDock tool.

The binding sites were defined by choosing grid boxes of suitable dimensions around the bound co-crystal ligands.

Molecular Interaction Analysis

Using the Graphical User Interface programme AutoDock Tools, intermediary steps were carried out, such as creating grid boxes and creating pdbqt files for protein and ligand preparation (ADT). AutoDock saved the prepared file in PDBQT format. Auto Grid was used for the preparation of the grid map using a grid box. The grid size was set to 60 × 60 × 60 xyz points with grid spacing of 0.375 Å and grid center was designated at dimensions (x, y, and z): -1.095, -1.554 and 3.894.

To reduce processing time, a scoring grid is created from the ligand structure. Utilizing protein and ligand information as well as grid box properties from the configuration file, Autodock Vina was used for docking. The iterated local search global optimizer is used by Autodock Vina. The pose with lowest energy of binding or binding affinity was extracted and aligned with receptor structure for further analysis.

Toxicophore Identification

Scaffold decomposition method was performed in order to identify the toxic moieties present in curated list of neurotoxins.It identifies common substructures among different molecules, which provides insights into their structural similarities and functional properties. Also, it can be used to compare different neurotoxins and identify the structural features that contribute to their toxicity. We performed scaffold decomposition using canvas platform of Schrodinger and the structure we retrieved was of cyclohexane. This indicates that the original molecules had a cyclohexane ring in its structure. The scaffold decomposition process helped to simplify the complex molecule into smaller fragments, making it easier to analyze and understand its properties. Overall, the scaffold decomposition process using the canvas platform of Schrodinger has provided valuable insights into the structural properties of the original molecule. We have reviewed the results to double check the retrieved toxicophore using the Python programming language, the machine learning toolkit (RDKit), and libraries, including Pandas (Python module), Preferred Installer Programme (PIP), and Python Imaging Library (PIL).

Blood Brain Barrier Penetration

The blood-brain barrier, a unique characteristic of the blood vessels vascularizing the central nervous system, permits these vessels to strictly regulate the transit of ions, chemicals, and cells between the blood and the brain [14]. The blood-brain barrier (BBB) limits the ability of many medications intended for the central nervous system (CNS) to exert therapeutic effects in the brain [15]. Neuroactive compounds should cross the BBB in order to be functional. In this study, we predicted the BBB penetration levels of the neurotoxins and the identified structural alert using SwissADME [16].

Global Reactivity Parameter Analysis

Using Gauss view density functional theory, we calculated global reactivity parameters analysis as a toxicity parameter. It is a valuable tool in predicting the toxicity levels of chemical compounds. We calculated key parameters such as the chemical potential, electrophilicity, and homo-lumo energy gap, which are closely related to the reactivity of the compound. By analyzing these parameters, it is possible to gain insights into the potential toxicity of the compound and its possibleimpact on human health and the environment. This analysis provides

insight into the electronic structure and reactivity of molecules, which can help determine their potential to cause harm.

RESULTS AND DISCUSSION

Physicochemical Properties

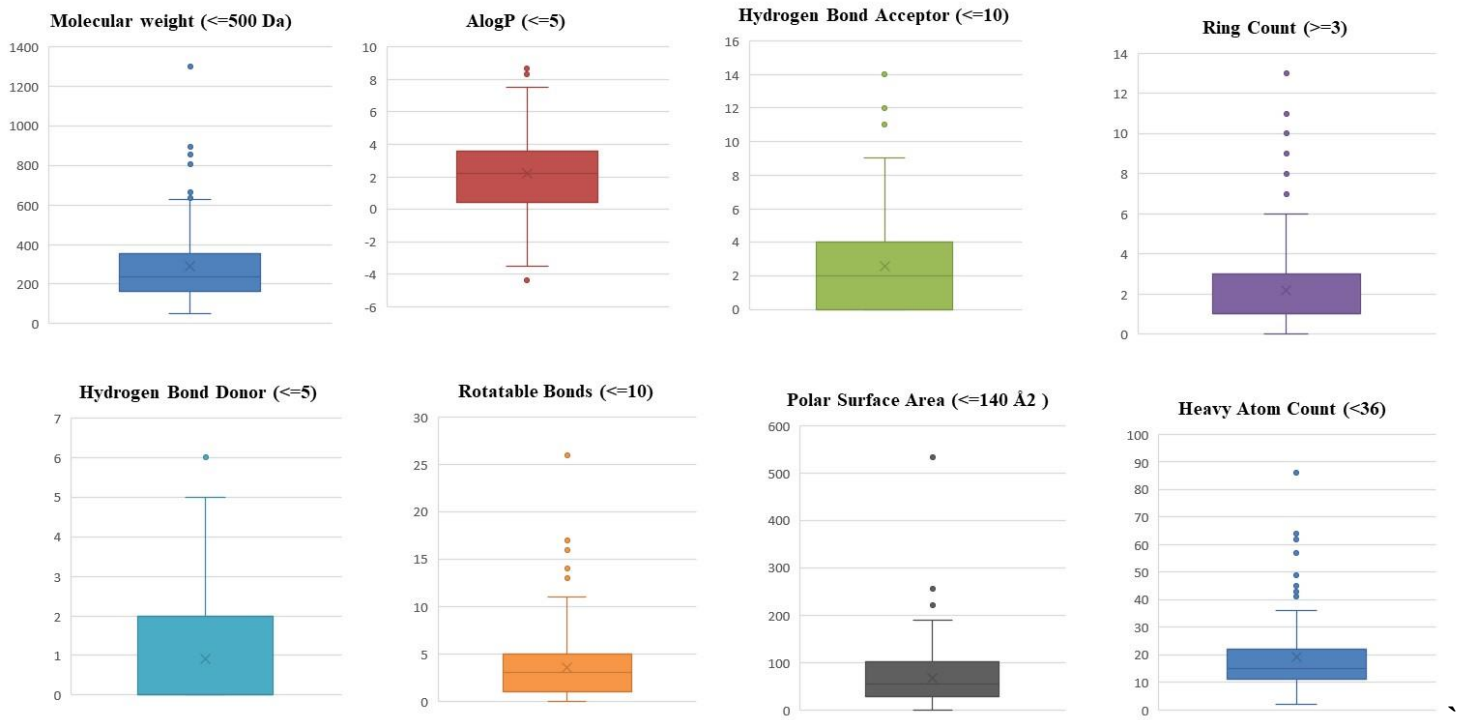


Figure2.Graphical representation of physicochemical properties of 161 neurotoxins

The physicochemical analysis of the 161 compounds (neurotoxins) revealed that 15 of them exceeded the polar surface area threshold, 15 exceeded the desirable value for heavy atoms, and 23 were above the ring count limit, which may indicate toxicity. Additionally, 23 compounds had molecular weights over 500, 17 showed AlogPabove 5, 6 exceeded the HBA cutoff, 2 exceeded the HBD cutoff, and 10 exceeded the RB cutoff. The box plots in figure 1 reveal that the favorable physicochemical parameters, along with the neurotoxins surpassing the recommended value.

Principal Component Analysis

Dimensionality is the number of features or variables present in the given dataset. PCA was done to reduce the dimensionality. It works by transforming correlated features into linearlly uncorrelated ones.It looks for lowest dimensionality surface to project high-dimensional data. The highest load of the dataset is molecular weight with co variance percentage of 93.88%. It is possible to depict the property space as a 3-D PCA plot because, as described in table 1, the first Principal Component (PCS) reflect 99.64% of the co variance, indicating that they

are acceptable to establish the property space. The first PC has the maximum Mol Wt load distribution(0.997) and nearly equal H acceptor, AlogP, and Rot Bond loadings. Mol PSA makes up the majority of the second PC, followed by H Acceptors and H Donors. The comparative PCA is shown in Table 2.These findings show that the property space is controlled by many characteristic parameters and significantly varies for the provided data. Thus; the first two principal components explain a majority of the total variance in the data.

Rstudio was employed to perform the PCA analysis and develop the plots using the respective R packages.

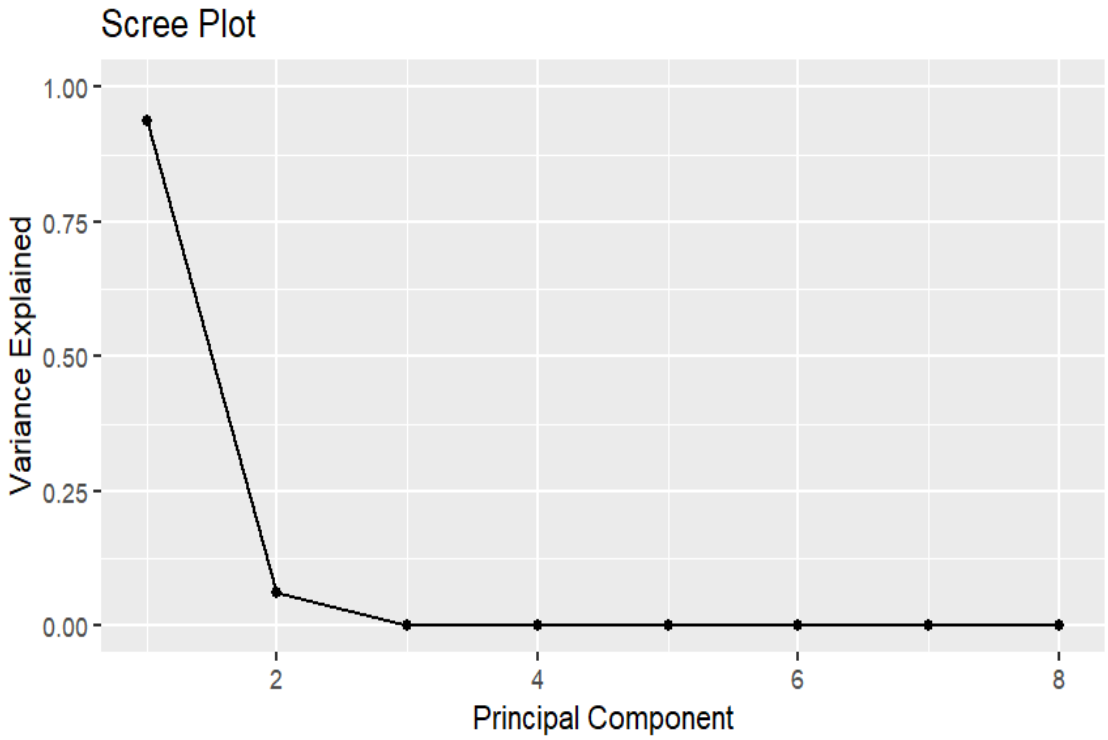


Figure 3. The scree plot showing the dominance of two components in the dataset

Table 1.Comparative principal component analysis (PCA) of physicochemical properties

Properties	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8
MW	-0.9778	-0.1998	0.0589	-0.0165	0.0121	-0.0076	0.0010	-0.0014
AlogP	-0.0062	-0.0311	0.0530	0.2559	-0.4404	0.8252	0.0468	-0.2315
HBA	-0.0108	0.0174	-0.2581	-0.0802	0.8319	0.4455	-0.0960	-0.1635

HBD	-0.0032	0.0129	-0.0419	-0.0332	0.0987	0.0663	0.9716	0.1970
RB	-0.0103	0.0096	0.0391	0.9183	0.1980	-0.2476	0.0745	-0.2212
PSA	-0.1987	0.9790	0.0281	-0.0056	-0.0277	0.0173	-0.0082	-0.0134
Heavy Atom Count	-0.0635	0.0119	-0.9236	0.1474	-0.2162	-0.0242	-0.0650	0.2636
Ring Count	-0.0090	-0.0057	-0.2644	-0.2483	-0.1318	-0.2321	0.1865	-0.8731

Table 2.Covariance of physicochemical properties

Properties	**PC1**	**PC2**	**PC3**	**PC4**	**PC5**	**PC6**	**PC7**	**PC8**
Variance	0.938784	0.060432	0.000394	0.000260	0.000066	0.000025	0.000024	0.000016
Percentage	93.88%	6.04%	0.04%	0.01%	0.00%	0.00%	0.00%	0.00%

Sankey's Diagram

The classification of the neurotoxins on the basis of targets is being represented by Sanky's diagram. It generally is a graphical representation depicting the flow of one set of attributes to other attributes. Neurotoxins are linked by their class and the diseases they target. Diazonian is a member of the group of organophosphates that target acetylcholinesterase and result in Myasthenia Gravis. Likewise, the terpene indole alkaloid, strychnine targets the serotonin receptor to cause convulsions. Understanding the specific targets of neurotoxins can provide insight into their mechanisms of action and potential therapeutic applications. By understanding the specific targets of these toxins, scientists can design drugs that block their effects and prevent symptoms from occurring. Additionally, this approach could also be used to identify new neurotoxins and potential treatments for other neurological disorders.

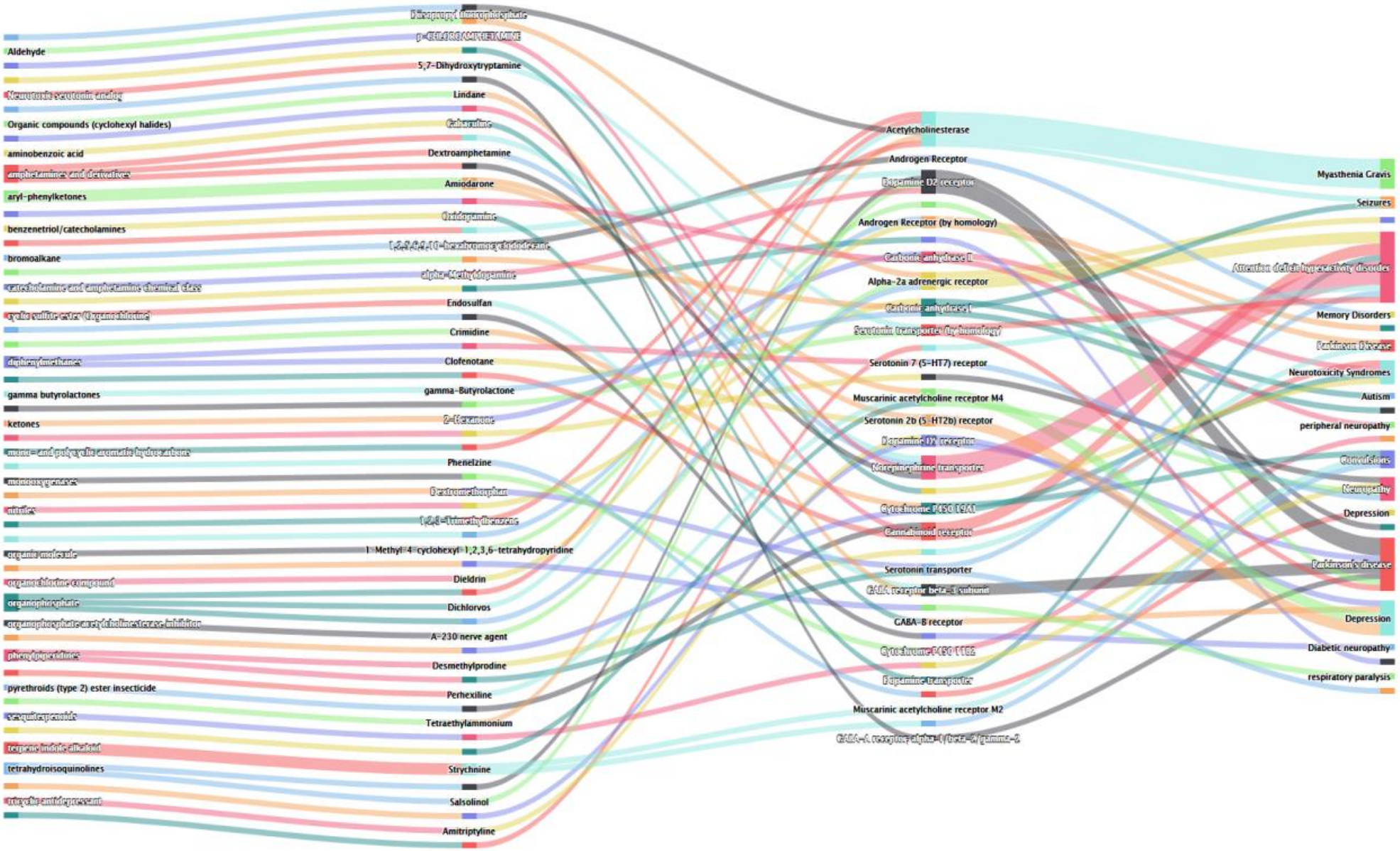


Figure 4: The flow of neurotoxins and target associated with the diseases shown by Sankey's diagram

Molecular Interaction Study

A docking study was utilized to better understanding of the structural basis of protein-neurotoxins interactions and to develop a hypothesis how the interactions could lead to disease progression. Docking analysis was performed on the neurotoxins against the following targets Acetylcholinesterase (1VZJ), Alpha-2a adrenergic receptor(6KUX), Androgen Receptor(1E3G), Cannabinoid receptor (6KPF), Carbonic anhydrase I (1A42), Cytochrome P450 1A2 (2HI4), Dopamine receptor (2QMZ), GABA receptor (7QN5), Muscarinic acetylcholine receptor M1 (6WJC), Norepinephrine transporter (3HCD), and Serotonin transporter (6VRH)

By analyzing the interactions between the molecule and the receptor, we were able to calculate the binding energy, which indicates the strength of the interaction between the neurotoxin and targets. The binding energy ranges from-5.4 kcal/mol to -10.5 kcal/mol of the complexes formed. With cannabinoid receptor, Kalkitoxin displayed -5.4 kcal/mol (6KPF) binding energy which suggest that possible nervous system disorders could arise from disruption to the cannabinoid receptor mechanism due to its interaction with Kalkitoxin. Strychnine formed a complex with the serotonin receptor (6VRH), showing the highest binding energy of -10.5 kcal/mol. Their interaction may lead to increased or decreased levels of serotonin, causing muscle spasms, muscle cramps, stiffness and tightness, agitation, heightened awareness and responsiveness, respiratory failure, stimulation-sensitive seizures, and possibly death. Also, the binding of strychnine to the serotonin receptor may also affect mood, appetite, and sleep patterns due to its impact on serotonin signaling in the brain. Chronic exposure to low levels of strychnine may also cause long-term changes in mood and behavior as a result of altered serotonin signaling.

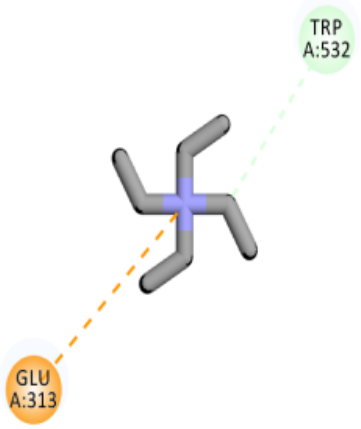
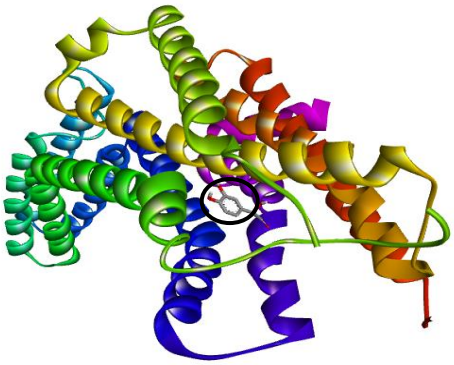
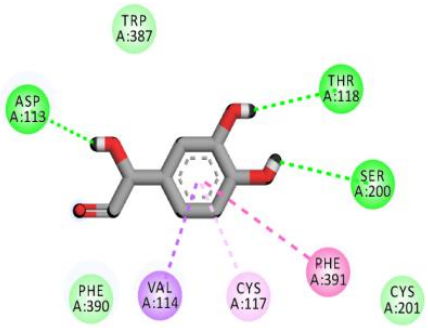
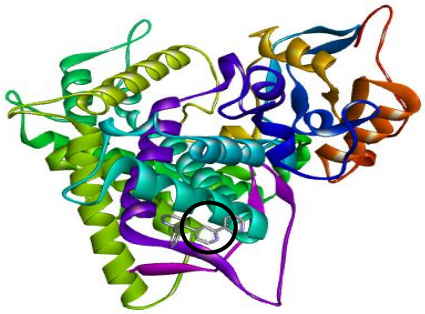
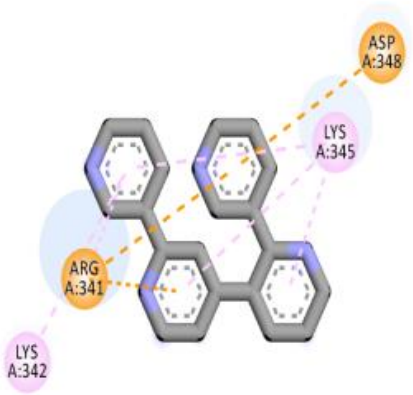
Table 3: Binding energy of neurotoxins with their respective targets given in kcal/mol.

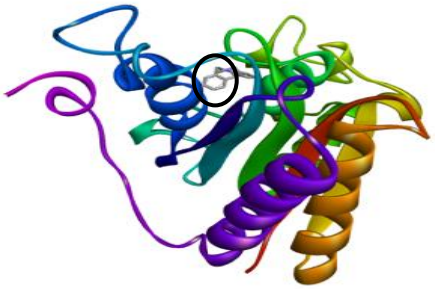
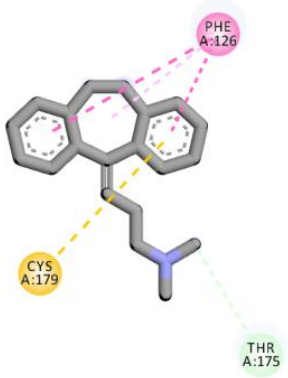
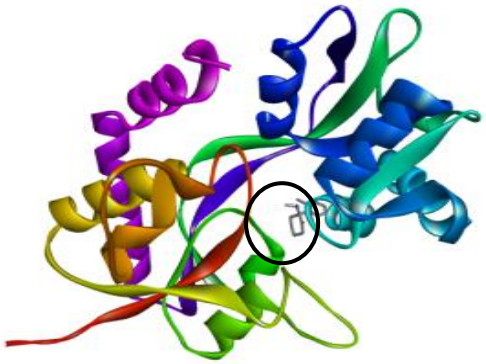
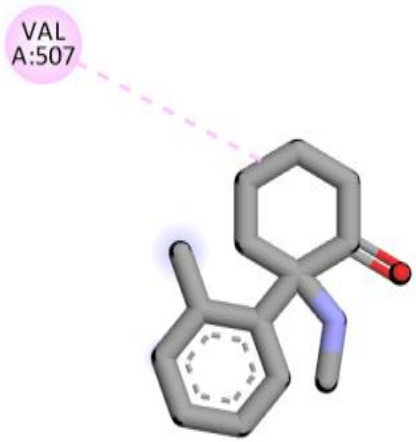
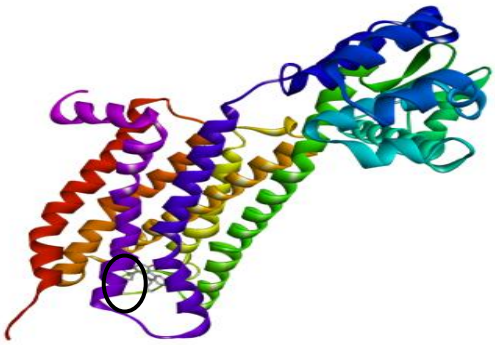
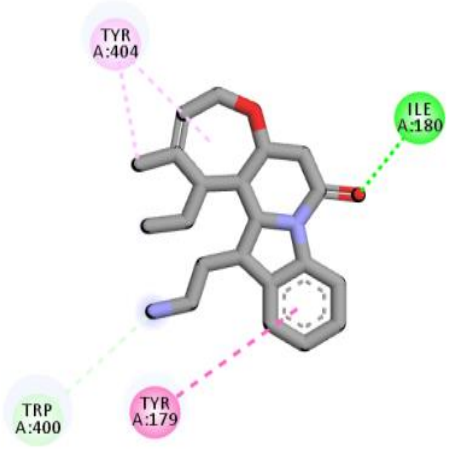
Neurotoxins	Targets	Binding Energy(kcal/mol)
Toluene	Acetylcholinesterase (1VZJ)	-5.4
Diisopropyl fluorophosphate		-6.2
Dichlorvos		-4.4
1,2,3-Trimethylbenzene		-5.1
Diazinon		-6.6
Tetraethylammonium		-3.9
3,4-Dihydroxymandelaldehyde	Alpha-2a adrenergic receptor (6KUX)	-6.2
A-230 nerve agent		-4.5
Mipafox		-5.3

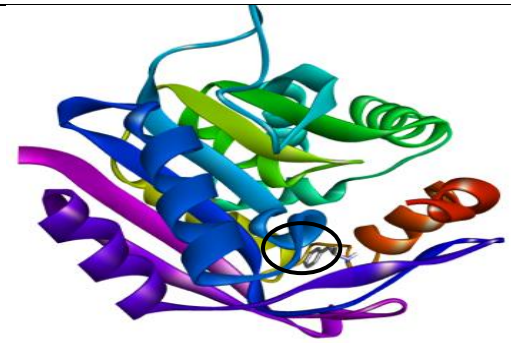
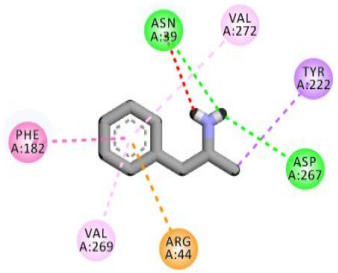
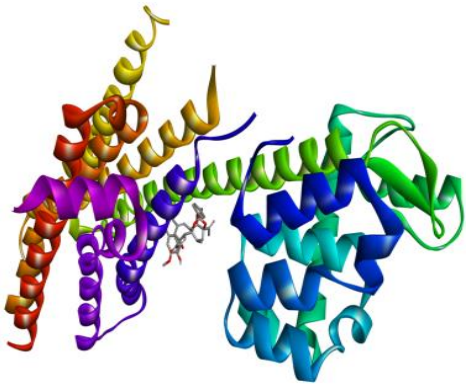
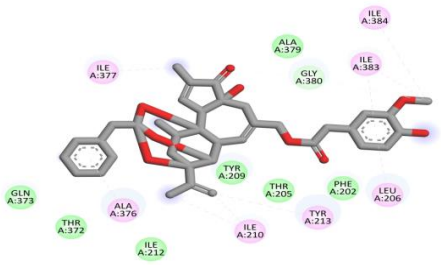
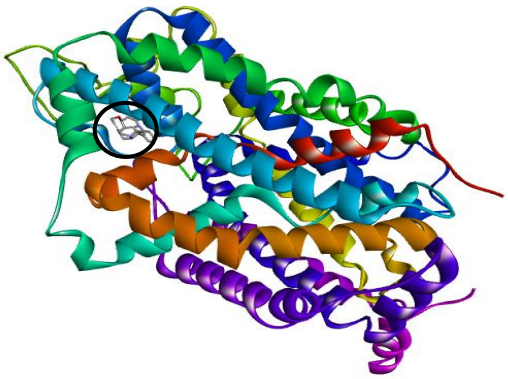
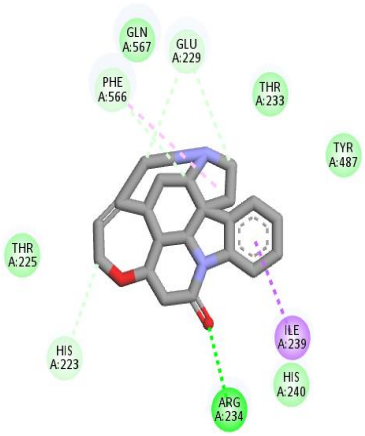
1,2,5,6,9,10-hexabromocyclododecane	Androgen Receptor (1E3G)	-2.7
2,5-Hexanedione	Androgen Receptor (1E3G)	-3.6
Dieldrin		-5.8
Kalkitoxin	Cannabinoid receptor (6KPF)	-5.4
Disulfoton		-3.5
gamma- Butyrolactone	Carbonic anhydrase I 1A42)	-3.9
3-Butenenitrile		-3.1
zinc;manganese(2+);N-[2-(sulfidocarbothioylamino)ethyl] carbamodithioate		-3.2
2-Hexanone		-3.8
N-Butylbenzenesulfonamide		-4.7
Nemertelline	Cytochrome P450 (2HI4)	-6.3
Crimidine		-4.9
Altretamine		-4.5
Phenelzine		-4.4
1-Methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol	Dopamine receptor 2QMZ	-5.6
Salsolinol		-5.8
1-Benzyl-1,2,3,4-tetrahydroisoquinoline		-6.6
alpha-Methyldopamine		-5.1
Desmethylprodine		-5.5
Amitriptyline		-6.9
Chlorprothixene		-6.3
Oxidopamine		-5.2
Endosulfan	GABA receptor	-5.7
Lindane		-4.6
beta-Methylamino-L-alanine		-4

Gabaculine	(7QN5)	-4.3
Caramboxin	Glutamate [NMDA] receptor (2ZNT)	-5.6
Ketamine		-6.2
Onchidal	Muscarinic acetylcholine receptor (6WJC)	-5.1
Strychnine		-8
2-Ethyl-8-methyl-2,8-diazaspiro(4,5)decane-1,3-dione		-5.5
Sertraline		-6.4
Perhexiline		-5.9
Amiodarone		-6.6
Fenitrothion		-4.9
p-Chloroamphetamine	Norepinephrine transporter (3HCD)	-4.2
p-Chloro-N-methylamphetamine		-4.2
Dextroamphetamine		-6.8
Amphetamine		-4.4
5-Methoxy-N,N-diisopropyltryptamine	Serotonin receptor (6VRH)	-5.3
Clofenotane		-8.6
Amiodarone		-6.1
1-Methyl-4-cyclohexyl-1,2,3,6-tetrahydropyridine		-5.7
Strychnine		-10.5
Dextromethorphan		-5.9
Glutethimide		-6
5,7-Dihydroxytryptamine		-4.7
Histrionicotoxin		-8.5
Resiniferatoxin	Dopamine D2 Receptor (6CM4)	-9.3

Table4. Representation of complex formed along with the active residues

	Complex Formed	2-D Ligand Interaction	Active residues
a			TRP A:532,GLU A:313
Acetylcholinesterase(1vzj) with Diazinon			
b			TRP A:387,THR A:118,ASP A:113,PHE A:390,VAL A:114,CYS A:117,PHE A:391,SER A:200,CYS A:201
Alpha-2a adrenergic receptor (6KUX) with 3,4Dihydroxymandelaldehyde			
c			ASP A:348,ARG A:341,LYS A:342,LYS A:345

Cytochrome P450 11B2 (2HI4) with Nemertelline			
e			PHE A:126,CYS A:179,THR A:175
Dopamine D5 receptor (2QMZ) with Amitriptyline			
f			VAL A:507
Glutamate NMDA receptor(2ZNT) with Ketamine			
g			TYRA:404,TYR A:179,TRP A:400
Muscarinic acetylcholine receptor M2 (6WJC) with Strychnine			

h			ASNA:39,VAL A:272,PHE A:182,VAL A:269,ARG A:44,TYR A:222,ASP A:267
Norepinephrine transporter(3HCD) with Dextroamphetamine			
			ALA:379,GLY:380,ILEA:383,ILEA:384,LEUA:206,TYRA:213,ILEA:210,ALAA:376,ILEA:377,GLNA:373,THRA:372,ILEA:212,TYRA:209,THRA:205.PHEA:202
Dopamine D2 receptor(6CM4) with Resiniferatoxin			
i			GLN A:567,GLU A:229,THR A:233, PHE A:566,THR A:225,HIS A:223,ARG A:234,HIS A:240,ILE A:239
Serotonin receptor (6vrh) with Strychnine			

In conclusion, molecular interaction studies point to the importance of hydrophobic interactions and non-polar bonding in maintaining the stability of complexes formed between neurotoxins and their target proteins.Aided by previous results according to C. Nick Pace, Hailong et al. (2011), these results allow us to reach the following conclusion: Molecular docking results contain the maximum number of residues with hydrophobic side chains.

Toxicophore Results

Depending on the molecular weight, the PCA-selected property, the neurotoxins underwent scaffold decomposition. Using software named Canvas, the result has been generated and interpreted using the identified scaffold. Additionally, it showed that the majority of the source structures contain the scaffold cyclohexane. Figures5.1 and 5.2 depicts the presence of a toxicophore or structural alert (indicated by the colour pink) in the source structures. The presence of the toxicophore in the source structures suggests a potential correlation between the scaffold cyclohexane and neurotoxicity. The Schrodinger canvas platform was used to disassemble the scaffolds, and it was discovered that the majority of them contained the Cyclohexane structure.

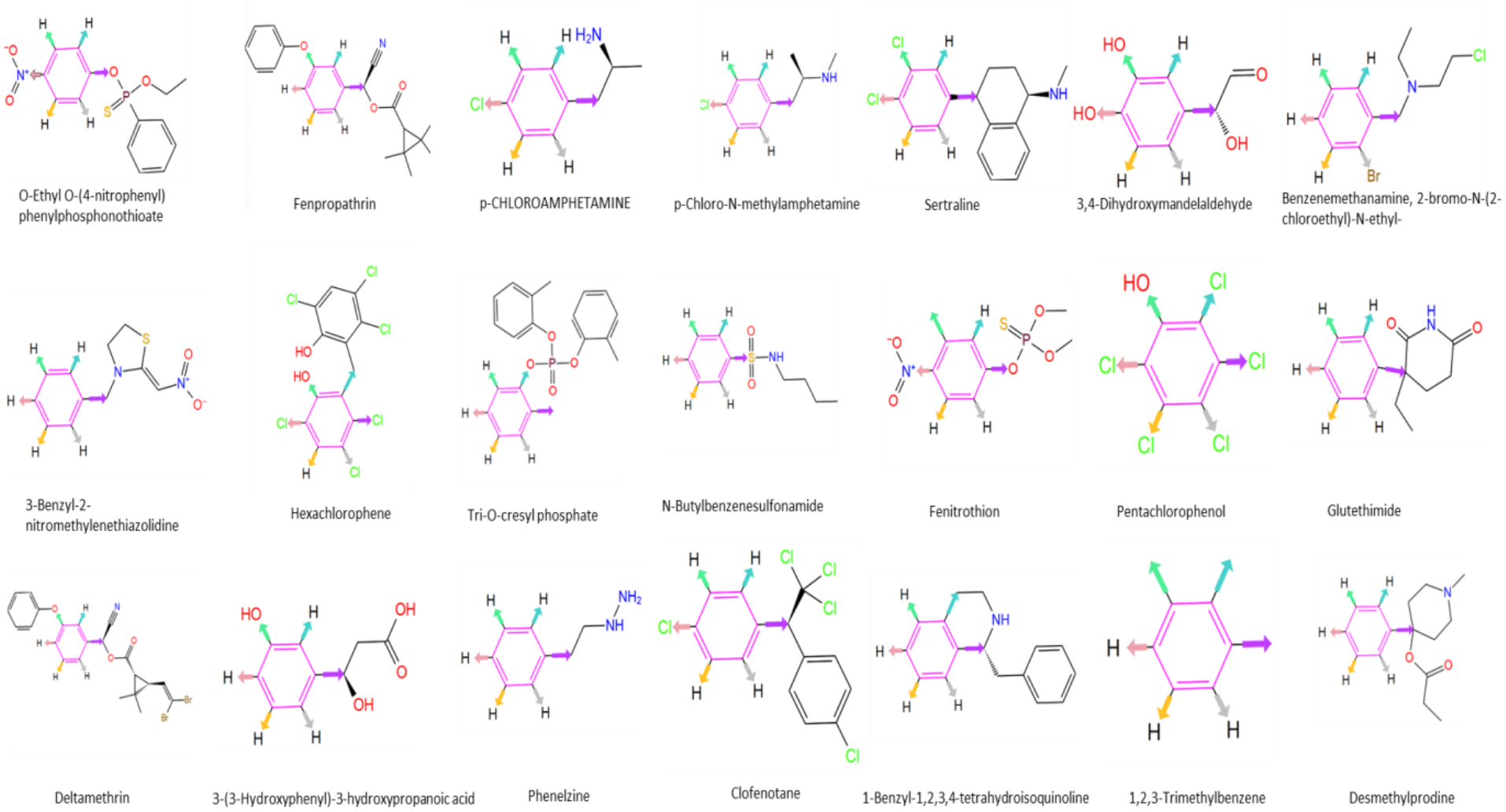


Figure5.1. Scaffolds generated using canvas:O-Ethyl-O-(4-nitrophenyl)phenylphosphonothioate,Fenpropathrin,p-Chloroamphetamine,p-Chloro-N-methylamphetamine,Sertraline,3,4 dihydroamandelaldehyde,Benzenemethanamine,2-bromo-N-(2-chloroethyl)-N-ethyl-,3-Benzyl-2-nitromethylenethiazolidine,Hexachlorophene,Tri-O-cresylphosphate,N-Butylbenzenesulfonamide,Fenitrothion,Pentachlorophenol,Glutethimide,Deltamethrin,3-(3-Hydroxyphenyl)-3-hydroxypropanoicacid,Phenelzine,Clofenotane,1-Benzyl-1,2,3,4-tetrahydroisoquinoline,1,2,3-trimethylbenzene,Desmethylprodine

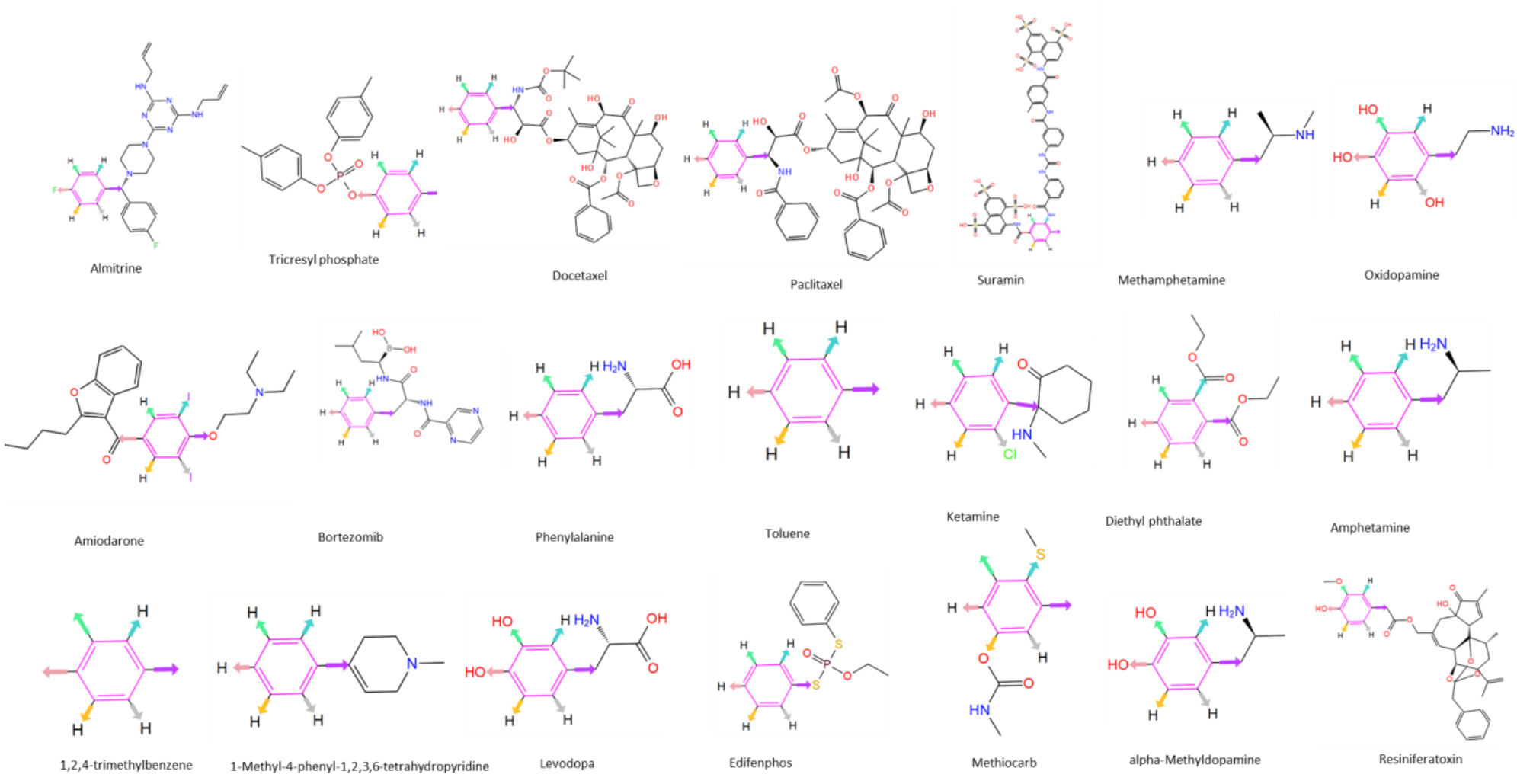


Figure5.2. Scaffolds generated using canvas:Almitrine,Tricresyl phosphate,Docetaxel,Paclitaxel,Suramin,Methamphetamine,Oxidopamine,Amiodarone,Bortezomib,Phenylalanine.Toluene,Ketamine,Diethyl phthalate,Amphetamine,1,2,4-trimethylbenzene,1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine,Levodopa,Edifenphos,Methiocarb,alpha-Methyldopamine,Resiniferatoxin

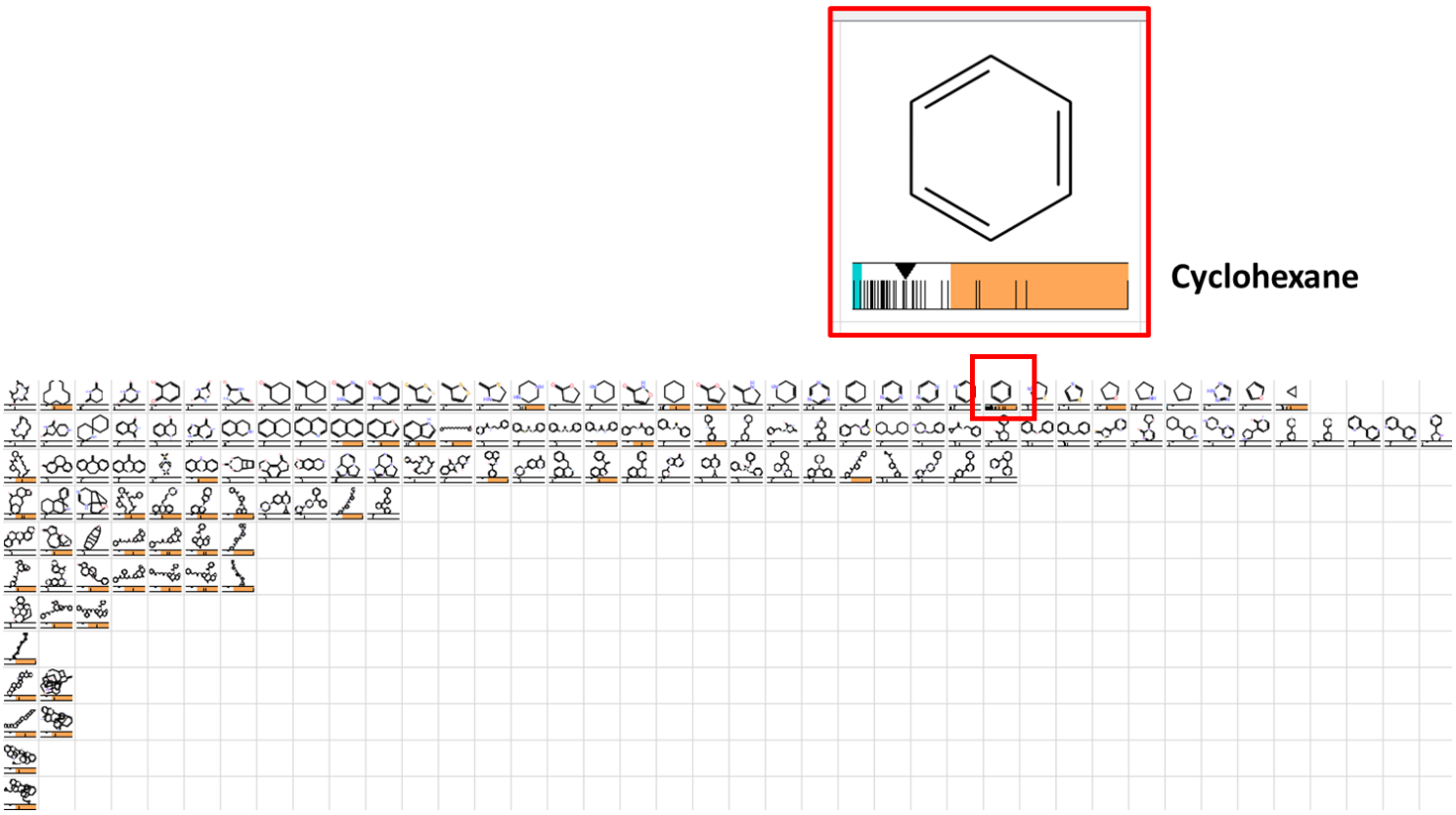


Figure6.Scaffolds obtained from selected structures and the scaffold shared by maximum source structures is highlighted.

People who use cyclohexane experience verbal memory loss, vertigo, limb weakness, headaches, and fatigue. Many of these things are drugs that are abused and have the potential to seriously harm neural tissue and impair neurological function. People who use cyclohexane experience verbal memory loss, vertigo, limb weakness, headaches, and fatigue. Recent research on mice has revealed that reactive gliosis, microglial reactivity, and oxidative stress are present in the brains of cyclohexane-exposed animals. This implies that cyclohexane might be harmful to the general public's health.For instance, individuals who abuse inhalants like paint thinner or gasoline are at risk of experiencing the same symptoms as those who use cyclohexane due to the presence of similar neurotoxic chemicals. Inhaling these substances can lead to permanent damage to the brain and nervous system, and in severe cases, even death. Therefore, it is crucial to raise awareness about the dangers of cyclohexane and other inhalants and to discourage their use (Campos-Ordonez *et al.*,2016).

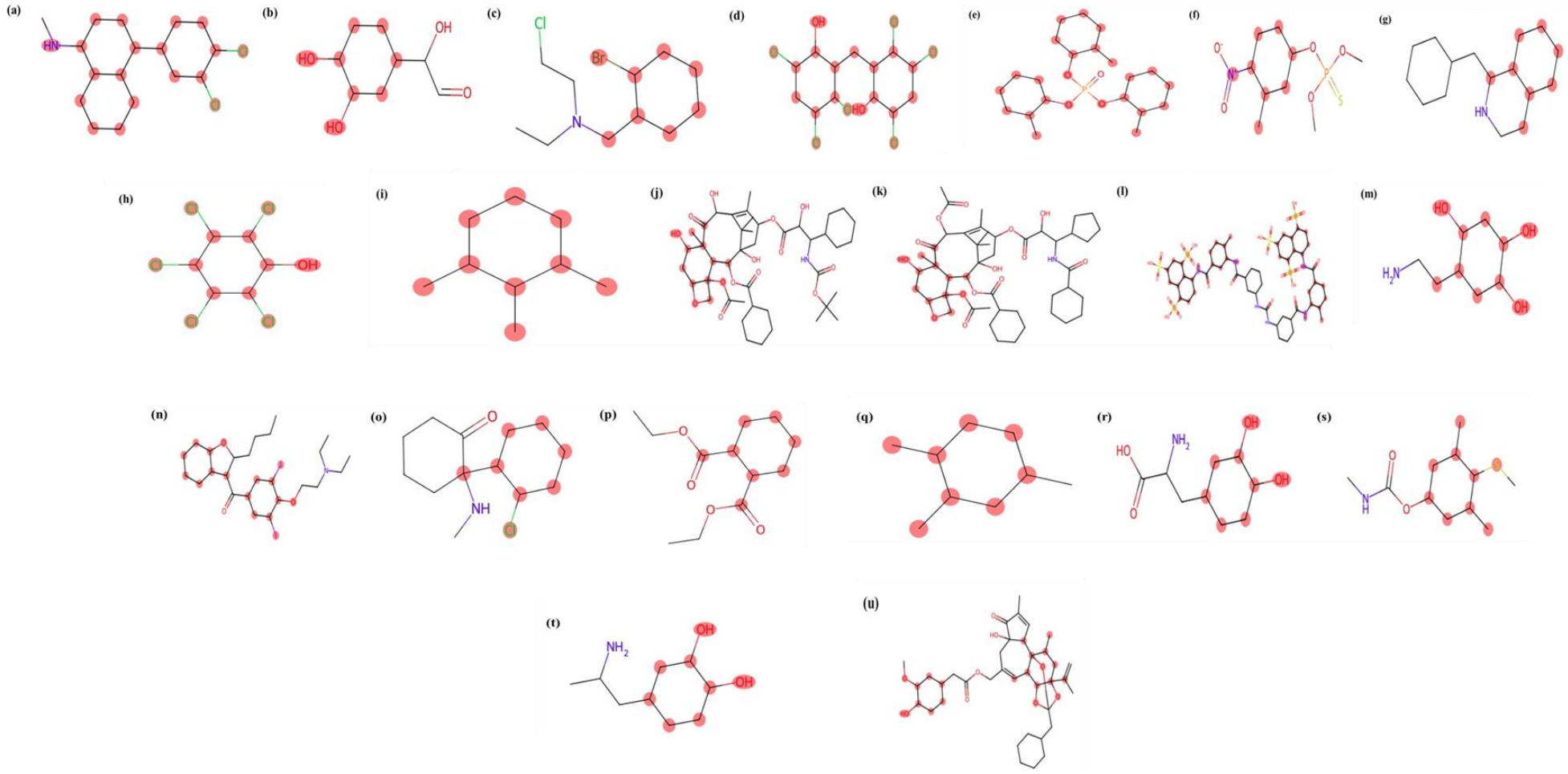


Figure 7. Using Python programming, a visual representation of neurotoxins with structural alert **(a)**Sertraline **(b)**3,4-Dihydrooxymandealdehyde **(c)** Benzenemethanamine, 2-bromo-N-(2-chloroethyl)-N-ethyl- **(d)**Hexachlorophene **(e)**Tri-O-cresyl phosphate **(f)**Fenitrothion **(g)**1-benzyl-1,2,3,4-tetrahydroisoquinoline **(h)**Pentachlorophenol **(i)**1,2,3- trimethylbenzene **(j)**Docetaxel **(k)**Palitaxel **(l)**Suramin **(m)**Oxidopamine **(n)**Amiodarone **(o)**Ketamine **(p)**Diethyl phthalate **(q)** 1,2,4-trimethylbenzene **(r)**Levodopa **(s)**Methiocarb **(t)**Aipha-Methyldopamine **(u)**Resiniferatoxin

Blood Brain Barrier Prediction

A vital biological barrier, the BBB tightly controls the environment of the CNS to promote healthy neuronal activity. The BBB is an important factor when deciding treatments for various neurological diseases because disruption of the barrier can cause severe pathology seen in a variety of diseases and because crossing the BBB is important for the development of the CNS -acting pharmaceuticals.Nearly 45% of the 163 neurotoxins that were collected, according to SwissADME findings, pass the BBB test, suggesting that they may play a significant role in the emergence of neurodegenerative diseases (see figure 8). The BBB for the structural alert (Cyclohexane) was also determined, and it showed that the barrier had been breached.

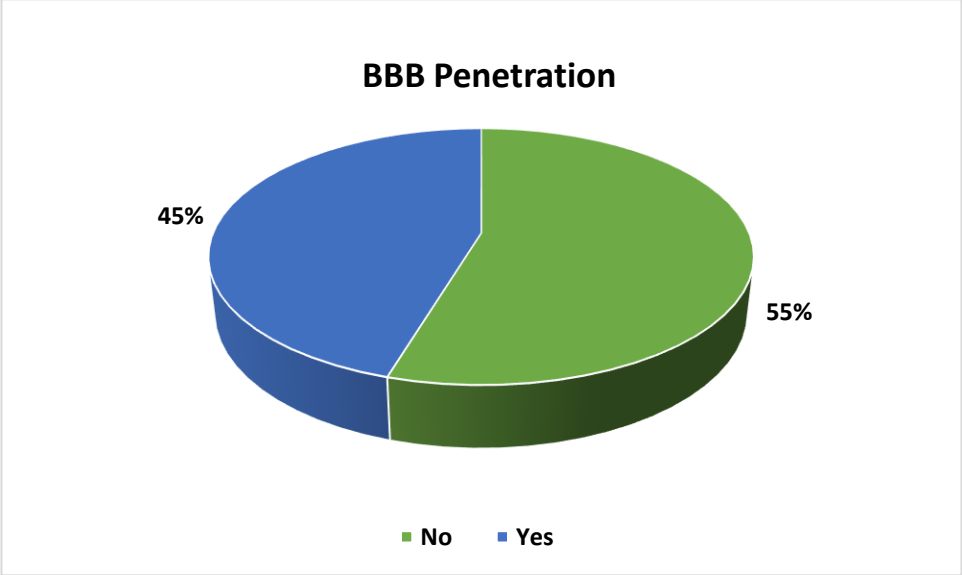


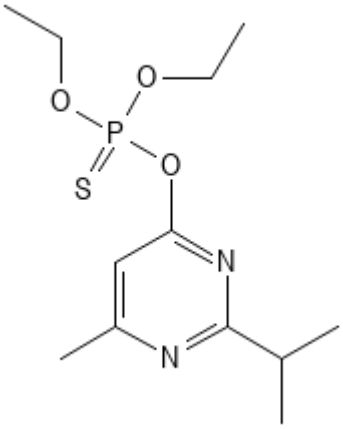
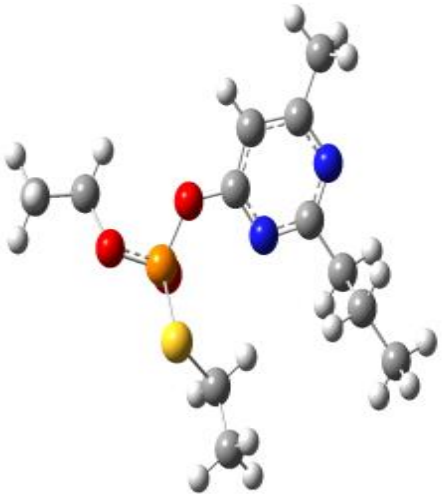
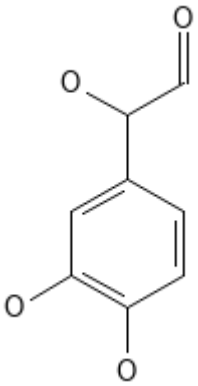
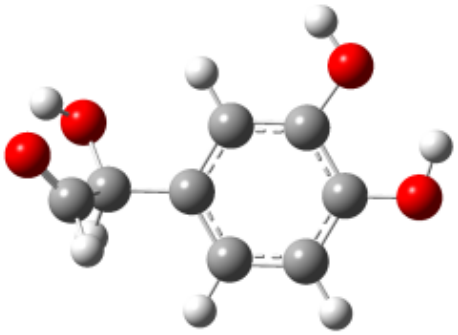
Figure 8. The graph depicts the percentile of BBB penetration of collected 163 neurotoxins using SwissADME

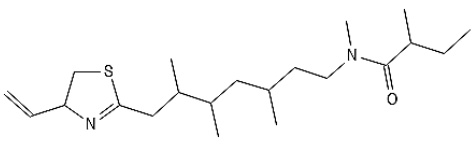
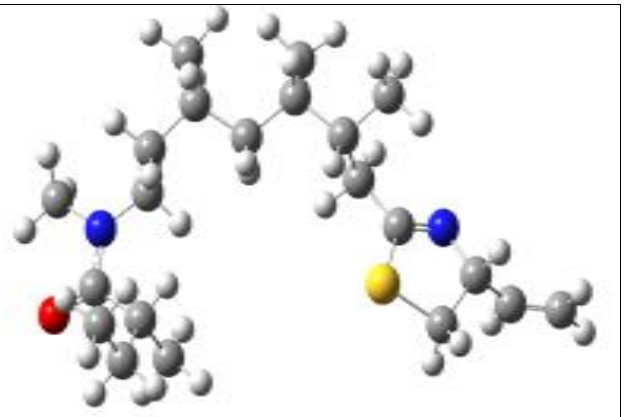
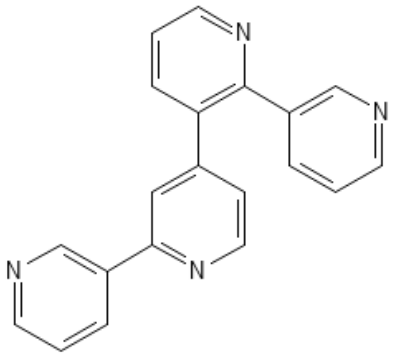
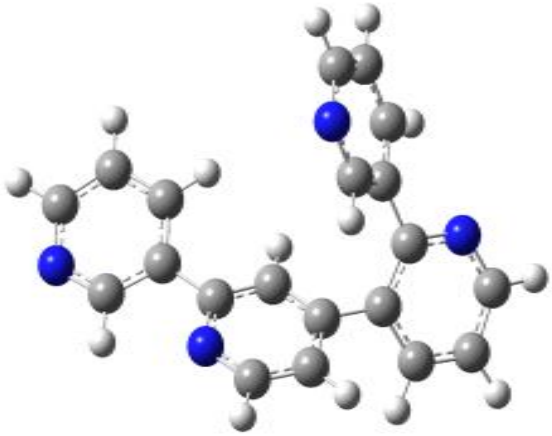
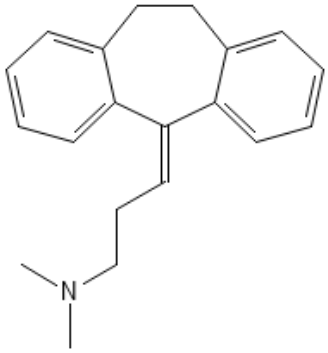
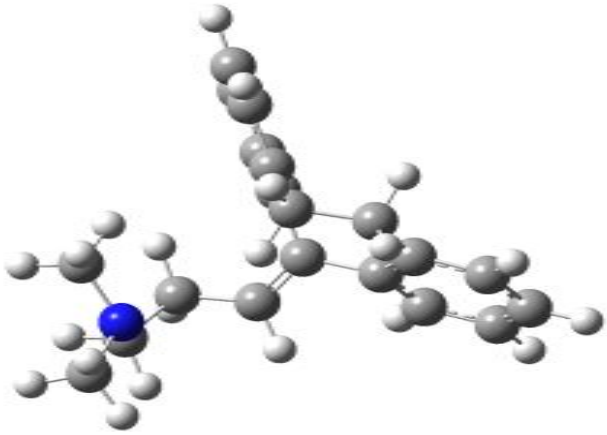
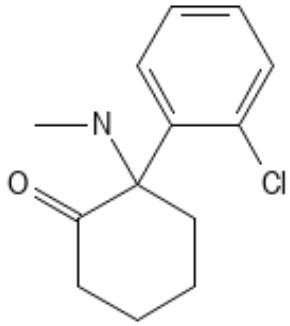
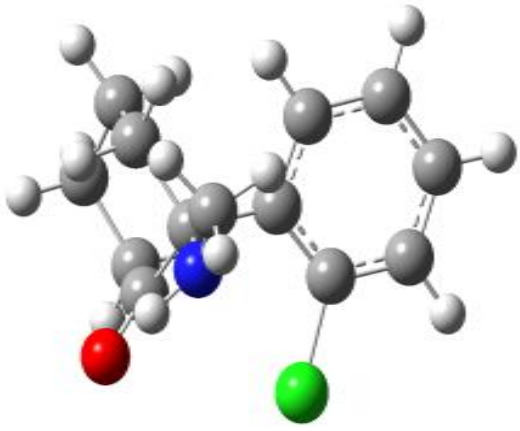
Global Reactivity Parameter analysis as a toxicity parameter

The global reactivity parameters analysis is a valuable tool for predicting the toxicity levels of chemical compounds. It allows for the calculation of key parameters such as the chemical potential, electrophilicity, and nucleophilicity, which are closely related to the reactivity of the compound. By analyzing these parameters, it is possible to gain insights into the potential toxicity of the compound and its potential impact on human health and the environment. It provides information on the chemical reactivity of a compound, which can help determine its potential to cause harm. This analysis provides insight into the electronic structure and reactivity of molecules, which can help determine their potential to cause harm. We can better understand how the compound will interact

with biological systems and potentially cause toxicity. Additionally, global reactivity parameters analysis can be used to compare the toxicity of different compounds and prioritize testing for those with the highest potential for harm. The electronic structure of atoms, molecules, and solids can be calculated using the DFT, a quantum-mechanical (QM) technique. Its objective is to quantitatively comprehend material properties using the basic principles of quantum mechanics.E_{HOMO} and E_{LUMO} (eV) values are acquired as a result of this study. $E_{HOMO-LUMO}$ (eV), Ionization Potential (IP), Electron Affinity (EA), Chemical Hardness (η), Global Softness, Chemical Potential (μ), Electronegativity (χ), and Electrophilicity Index (ω) have all been derived using these two parameters which were shown in Table 6.The Optimized Gaussian Structure of the compounds are shown in Table 5.

Table 5: Pictorial representation of optimized Gaussian Structure

Name of Compound	2D Structure	Optimized Gaussian Structure
Diazinon		
3,4-Dihydroxymandelaldehyde		

Kalkitoxin		
Nemertelline		
Amitriptyline		
Ketamine		

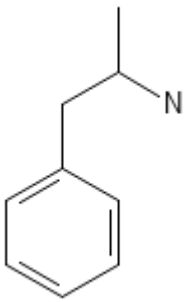
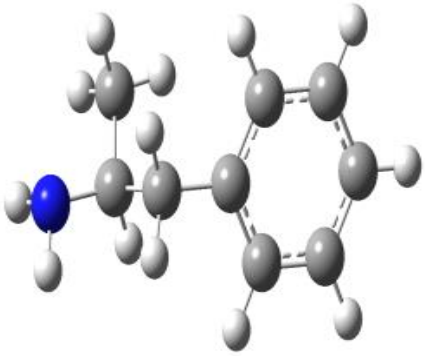
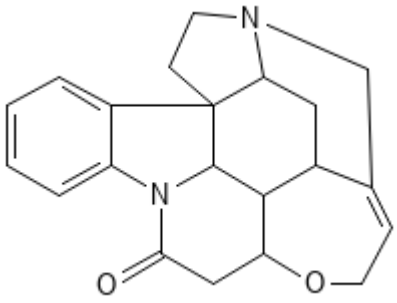
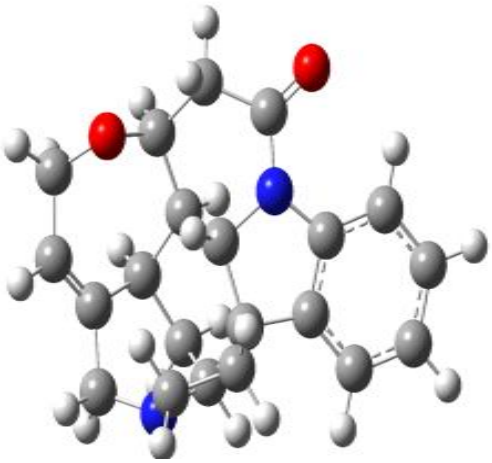
Dextroamphetamine		
Strychnine		

Table 6. Calculated energy values of screened best 8 compounds using B3LYP/6-311G(2D,P)

NEUROTOXIN	HOMO (Ev)	LOMO (Ev)	EHUMO-LUMO (Ev)	IP	EA	CHEMICAL HARDNESS (η)	CHEMICAL SOFTNESS	CHEMICAL POTENTIAL (μ)	ELECTRO NEGATIVITY (χ)	ELECTRO PHILICITY INDEX (ω)
Diazinon	-7.129	-0.836	-6.292	7.129	0.836	3.146	0.159	-3.146	3.146	1.573
3,4-Dihydroxymandelaldehyde	-5.799	-1.198	-4.601	5.799	1.198	2.301	0.217	-2.301	2.301	1.150
Kalkitoxin	-6.246	-0.241	-6.005	6.246	0.241	3.003	0.167	-3.003	3.003	1.501
Nemertelline	-6.506	-1.690	-4.816	6.506	1.690	2.408	0.208	-2.408	2.408	1.204
Amitriptyline	-5.668	-0.398	-5.270	5.668	0.398	2.635	0.190	-2.635	2.635	1.317
Ketamine	-5.686	-0.534	-5.152	5.686	0.534	2.576	0.194	-2.576	2.576	1.288
Dextroamphetamine	-6.304	0.506	-6.810	6.304	-0.506	3.405	0.147	-3.405	3.405	1.702
Strychnine	-5.531	-0.185	-5.346	5.531	0.185	2.673	0.187	-2.673	2.673	1.336

Homo Lumo energy

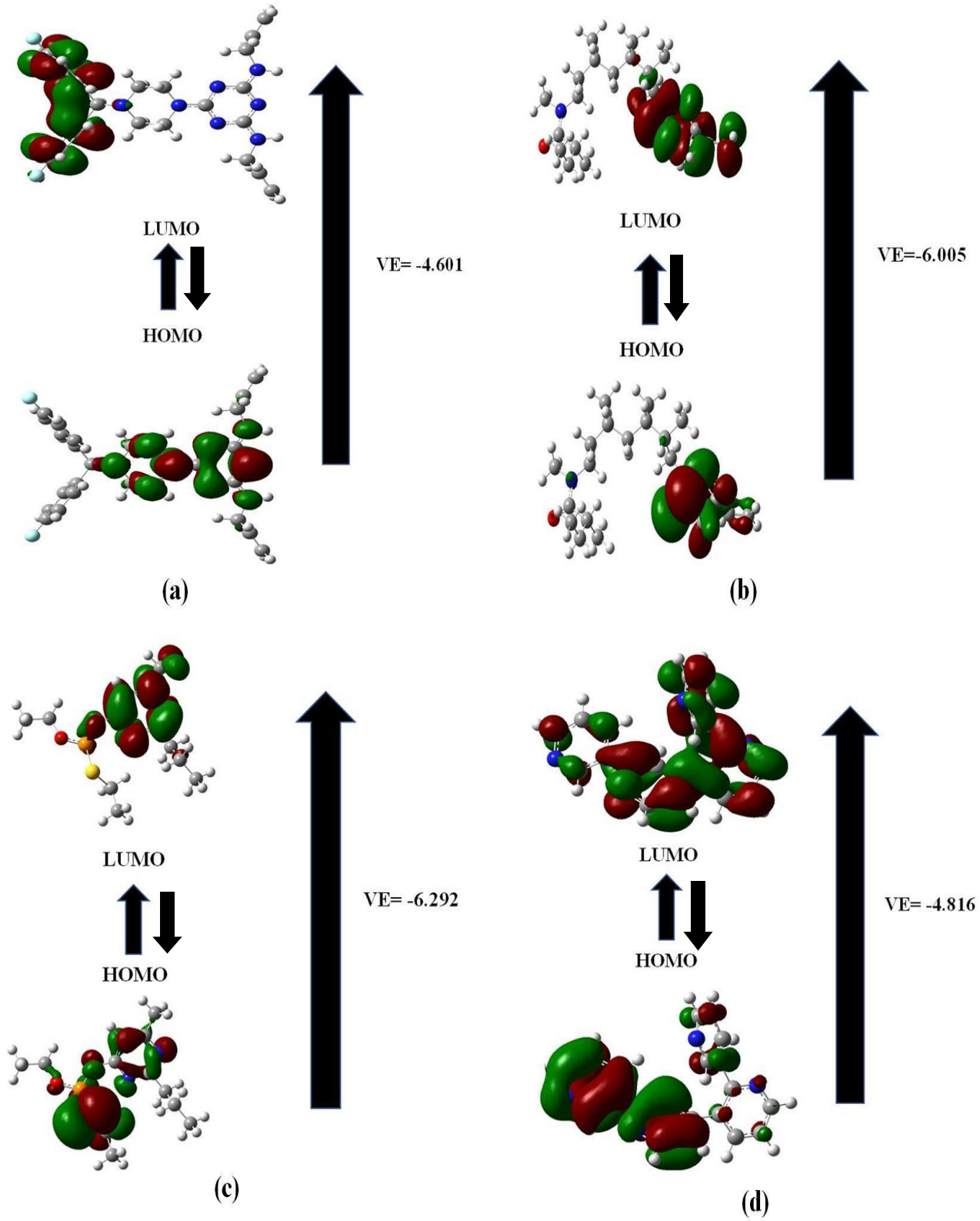


Figure 9.1: DFT-Optimized Frontier molecular orbitals and HOMO-LUMO energy gaps for a)3,4-Dihydroxymandelaldehyde b)Kalkitoxinc)Diazinon d)Nemertelline

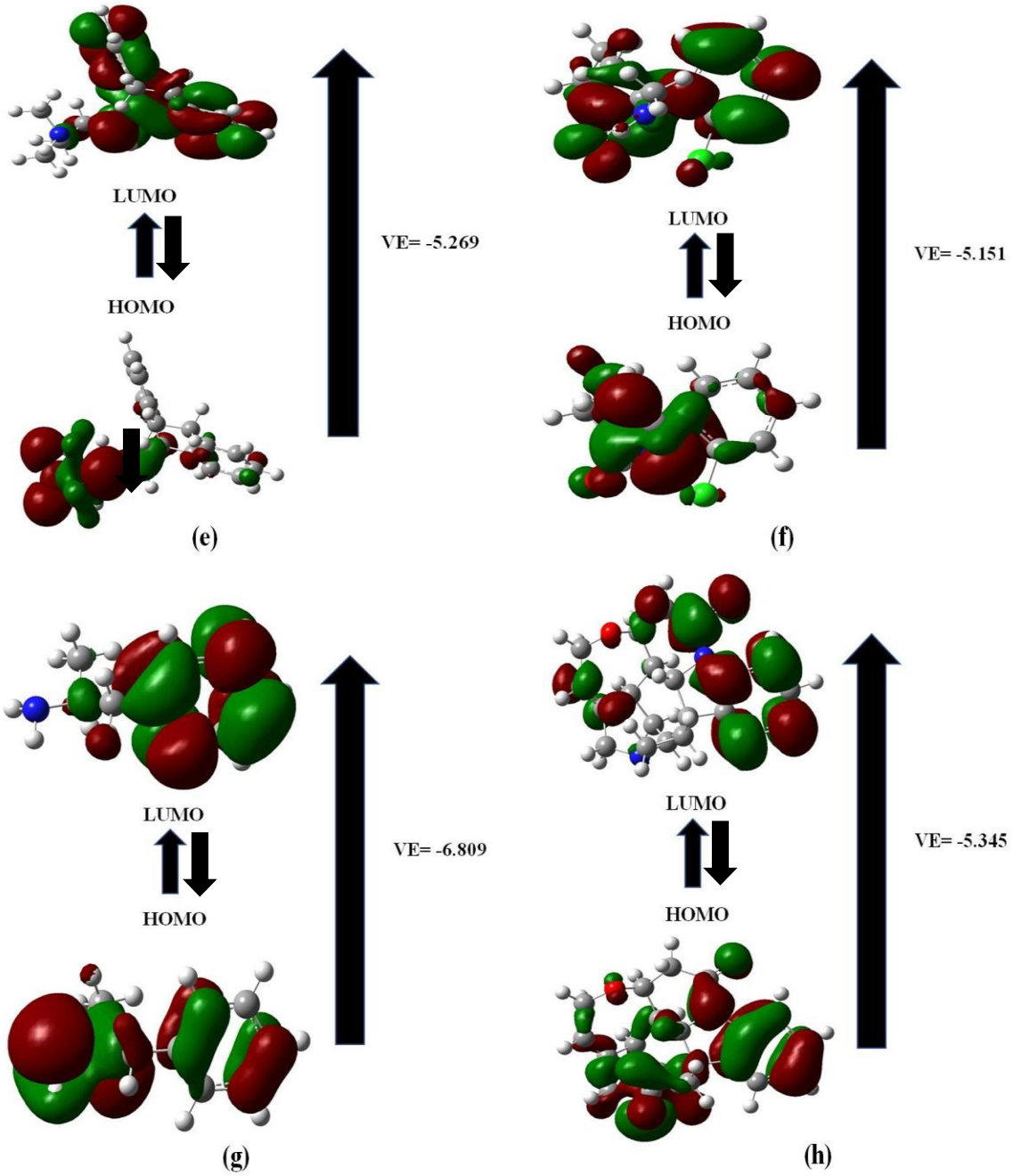


Figure 9.2: DFT-optimized Frontier molecular orbitals and HOMO-LUMO energy gaps for e) Amitriptyline f) Ketamine g) Dextroamphetamine h) Strychnine.

The structure of dextroamphetamine represented the highest homo lumo energy gap with -6.8 Ev while the lowest was found in the structure of Kalkitoxin with gap of -4.6 Ev. These calculated values provide valuable insights into the reactivity and stability of molecules. The large energy gap in dextroamphetamine indicates its potential for high chemical stability, while the smaller gap in Kalkitoxin suggests a higher likelihood of chemical reactivity and potential neurotoxic effects.

CONCLUSION

Neurological disorders may damage the brain, spinal cord, or other nerves. Among these problems include decreased mobility, weakened muscles, cognitive impairment, and difficulty doing routine regular tasks. In addition, dealing with the difficulties of a debilitating and progressive illness can take a tremendous emotional and psychological toll on the patient as well as their loved ones.Numerous neurologic conditions that are incurable may experience foreseen issues in the course of the disease or in its final stages. Even though there is no known cure, ongoing studies and improvements in medical technology give hope for better management and symptom relief in the future.

The study identified the structural alert, Cyclohexane present in the majority of source structures. By incorporating numerous Python packages, such as RDKit (Machine Learning Approach), Pandas, and PIL (Python Imaging Library), we have validated or cross-checked the scaffold by machine learning approach.As a result, we were able to obtain 21 compounds that contain cyclohexane as a warning sign for neurotoxicity.A careful examination of the data reveals that toxicophore allow for the identification of compounds that cause neurotoxicity.Additionally, we checked the blood brain barrier for any accumulated neurotoxins. SwissADME allowed us to extract 45% of the 163 neurotoxins, demonstrating that it can be neurotoxic. Determine the BBB parameters for the alert or toxicophore, which results in favorable BBB permeation and might be a reliable indicator of neurotoxicity. Long term exposure to organic solvents may also result in chronic encephalopathy, a condition marked by abnormalities in the structure of the brain and cognitive dysfunction.

Demonstration of how ligands and receptors interact at molecular level may be useful for designing the drugs of the non-targeted or undruggable neurological targets. Our results have shown plausible binding affinity of neurotoxins with their respective targets and the study has elucidated the possible molecular interactions of aforesaid compounds. It is deciphered that the binding deregulates the normal functioning of the receptors hence, the neurological disorders prevail. Our findings suggested that neurotoxins had reasonable binding affinities for their specific targets, and the research clarified potential molecular interactions of the listed substances. It has been determined that since binding disrupts the receptors' normal function, neurological problems emerge. Neurotoxicity is one of the not well understood areas of study. Most of the time, the failure of the drug development process is caused by a lack of knowledge about the molecular target and how it interacts with toxins It is important to understand the presence of cyclohexane in neurotoxins as it can help in developing strategies to mitigate their harmful effects and ensure the safety of individuals exposed to these toxins. The presence of cyclohexane in neurotoxins is a crucial factor to consider in developing strategies to mitigate their effects and

ensure the safety of those exposed to these toxins. However, further research is needed to fully understand the mechanisms of cyclohexane toxicity and its role in neurotoxicity.

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