CHAPTER 2
Survey of literature

The fundamental assumption of QSAR is that the variation in biological activity of a series of chemical compounds that target a common mechanism of action are correlated with variation in their structural, physical and chemical properties. These properties can be determined by experimental or computational methods. Since, a statistically validated QSAR model is capable of predicting the biological activity of a new compound within the same series in lieu of the time consuming and labour intensive process of chemical synthesis. Applied judiciously, QSAR modelling can have substantial amount of time, money and human resources. QSAR models are now regarded as a scientifically credible tool for predicting and classifying the biological activity of untested chemicals especially in the field of pharmaceutical industry, from the lead discovery and optimization to lead development [1-4].

It is a well known fact that the different properties exhibited by a chemical compounds are the function of their chemical structures. Quantitative study of activity or property or toxicity related to structure of chemical compound, methodology is known as quantitative structure-activity/property/toxicity relationship (QSAR/QSPR/QSTR). Such methodologies are investigated and used for more than fifty years to combine parameters [5-12].

To initiate QSAR study, among different methodologies QSAR study can be understood in terms of

1. Types of target property
2. Types of descriptors
3. Types of optimization algorithm used to relate design to target properties.

On the basis of (1) a continuous range of values are used for the purpose of subsequent analysis are referred.

Types of descriptors (2) used are based on mode of generation. Descriptors can be generated from various representations of molecules giving rise to terms of
2D, 3D QSAR respectively. These terms further include 2D chemical groups or 3D molecular geometries and to higher range successively.

Finally (3) used in QSAR model development leads to two main streams as linear and non-linear QSAR methods. It is observed that in many cases (1), (2) and (3) are closely related and mutually inclusive. However this leads to one more categorization of QSAR methodology in terms of multiple-linear regression and partial least square techniques [13,14].

MLR can be applied only in case of use of a relatively small number of molecular descriptors. It is always preferred to use molecular descriptors/topological indices five to six times smaller than the total number of compounds [Thumb rule] [15, 16] and in additives to this the target property is characterized by a continuous range of values. It is observed that consequences of violation of Thumb rule may appear in form of high chance of spurious correlation. Method of Partial list square (PLS) offers an excellent solution to this problem. This method is also known as non-linear optimization technique [17-23].

Computer-aided QSAR study of some CNS acting drugs is attempted to obtain statistically validated QSAR models, capable of predicting the biological activity. The predictive power of QSAR models critically depends on statistically quality of the data used to develop the model and estimated its parameters to calculate biological activity in quantitative manner. Attempts in this direction are made by our group to study QSPR as well as QSTR [24-33]. QSAR, QSPR as well as QSTR studies are considered as significant tools for predicting physical, chemical properties in almost all the scientific fields. QSAR also represented to involve the use of spectroscopic data by our group [34, 35]. Our group attempted spectroscopic studies and observed that X-ray absorption spectra provide an experimental indication of how the electronic environment of the absorbing metal change as the consequence of complex formation. This study included K-absorption discontinuity of the metal changes during complex formation. As it is well established [34-54] that complex formation remained throughout intensive, exciting as well as important phenomenon to human physiology and biological activity of chemical compound, it is the reason that our group has undertaken it for extensive studies. It is the worthy to mention that our group has studied lipophilicity in relevance of computer-aided drug design and re-
ported extensively \cite{55} as a review of literature. Hydrophobicity, proton-ligand formation constant, particle research environmental are also reported by us \cite{56-58}. The novel guide lines in view of topological modelling of physicochemical property using molecular connectivity in drug designing and structure activity analysis reported by Kier and Hall \cite{59,60} provided as milestone to many generations of researchers.

Significant QSAR approach in various fields are attempted and reported by Shobha Joshi and co-workers, under the leadership of late Professor PV Khadikar \cite{61-77}. As mentioned, after the successful attempts of our group to develop QSAR/QSPR/QSTR of some drugs/compounds of interest in pharmaceutical chemistry and other fields has opened a new era to work to this aspect, CNS acting drugs exhibiting neuroactive profile.

Accumulation of excess senile plaques (β-amyloid, Aβ-plaques) in the brain is strongly associated with the pathogenesis of Alzheimer disease (AD) \cite{78}.

Several groups have reported potential imaging agents for the in vivo imaging of Aβ-amyloid plaques with positron emission tomography (PET). Mi Kyoung Kim, H. Han choo et al. \cite{79} constructed 3D QSAR model with several PET ligands such as Thio T analogues and stilbene derivatives.

**Positron emission tomography (PET) agent**

A strong imaging agent for Aβ plaques in the brain should have ability to rapidly penetrate the blood-brain barrier. Agent’s binding affinity, selectivity and blood clearance ability should be high. It should have high initial brain uptake and fast washout from the normal brain \cite{80,81}. Many PET agents targeting Aβ plaque penetrates the brain but not show specific binding \cite{82-84}. Some highly conjugated dyes Thioflavin T and stilbene can be used for fluorescent staining of plaques \cite{85-87}. These molecules displayed desirable properties like high binding affinity and ability to cross blood brain barrier (BBB). In vitro studies suggested that amyloid plaques have multiple binding sites, so they can bind structurally different compounds.

In 1959 luminous dye Thioflavin-T (Thio T) was first described as selective staining agent and able to identifying amyloid fibrils. Thio T binds rapidly to the anti-parallel beta-sheet fibrils of peptide, but it does not show binding with mono-
mer. Rotation around the central C-C single bond and restricted C-N bond rotation are responsible of Thio T’s detector activity \[88-90\].

It has been reported that systematic injection of Abeta peptide prevents the deposition of Abeta peptide \[91, 92\]. A group of chemists (Lippa, C.F., Schmidt, M.L., Nee, L.E., Bird, T., Nochlin, D.et al.) observed that AMY plaques are consistently present in familial AD due to presenilin-1 (PS-1), presenilin-2 (PS-2) and amyloid precursor protein mutations, and they can begin to accumulate before the emergence of dementia \[93\]. Cermeascu et al. identified a powerful technique Laser-induced liquid bead ion desorption mass spectrometry (LILBID MS), that will advance the understanding of peptide oligomerization in neurodegenerative diseases and represents a powerful tool for the identification of small oligomerization inhibitors \[94\]. Portelius E. et al. reported that the concentration of the 42 amino acids form of Aβ (Aβ1-42) reduce in the cerebrospinal fluid (CSF) from AD patients, which is believed to reflect the AD pathology with plaques in the brain acting as sinks. Recently, novel C-truncated forms of Aβ (Aβ1-14, Aβ1-15, and Aβ1-16) were indentified in human CSF \[95-97\]. Nanoparticles affect amyloid aggregation, its effect depends on the protein stability and intrinsic aggregation rate, it can play role in treatment of Alzheimer disease \[98,99\]. Wang et al. reported qualitative and quantitative differences in senile plaque dystrophic neurites of Alzheimer's disease and normal aged brain and suggested that plaque-independent mechanisms of development of tau neurites operate in AD \[100\]. Synthesis and evaluation of ferrocenoyl pentapeptide (Fc-KLVFF) as an inhibitor of Alzheimer’s Aβ1-42 fibril formation in vitro carried to investigate the interaction between the inhibitor and Aβ(1-42) in real-time by electrochemical method \[101\]. It is further reported by Jan et al. that the ratio of monomeric to aggregated forms of Abeta40 and Abeta42 is an important determinant of amyloid-beta aggregation, fibrillogenesis, and toxicity \[102\]. Liu et al. discovered a new inhibitor to target the intermediate structure of beta-amyloid peptide on the conformational transition pathway and implicated in the aggregation mechanism of beta-amyloid peptide. They not only provided a strategy for inhibitor design based on the flexible structures of amyloid peptides but also revealed some clues to understanding the molecular events involved in Abeta aggregation \[103\]. Liu R et al. reported that Abeta aggregation can be inhibit by single chain variable fragments against beta-amyloid (Abeta) and thus abeta-induced neurotoxicity can be prevented \[104\].
Olesen OF had reported important role of tau and amyloid in Alzheimer’s disease [99]. According to Harigaya et al. Amyloid beta protein, starting pyroglutamate at position 3 is a major component of the amyloid deposits in the Alzheimer’s disease brain [97]. Sun et al. analyzed structure of the pyroglutamate - modified isoforms of the Alzheimer’s disease-related amyloid-β by NMR spectroscopy [96]. Meng et al. reported a novel strategy to dissociate amyloid aggregation, using localized heat generation from a clinically used amyloid staining dye, thioflavin-S (Thio S)-modified graphene oxide (GO) under NIR laser irradiation. In comparison of traditional chemotherapies photothermal therapy shows reduced side effects and improved selectivity and safety [105].

Vallabhjosula S. reported positron emission tomography (PET) by using [18F] fluorodeoxyglucose (FDG) for imaging brain Beta-amyloid [106].

Li et al. prepared novel cyclopentadienyl tricarbonyl Complexes of 99mTc that mimic the chalcone structure and reported them as Potential Single-Photon Emission Computed Tomography Imaging Probes for β-Amyloid Plaques in Brain [107]. Mengchao et al. synthesized novel 18F-Labeled Benzoxazole Derivatives as Potential Positron Emission Tomography Probes for Imaging of Cerebral β-Amyloid Plaques in AD [108]. Furthermore, Mengchao et al. synthesized and Evaluated Novel 18F labelled 2-Pyridinylbenzoxazole and 2-Pyridinylbenzothiazole Derivatives as ligands for Positron Emission Tomography (PET) for imaging β-Amyloid Plaques [109]. Singh et al. have examined fluorescence sensing activity of the Thioflavin T and reported that Thio T undergoes ultrafast bond twisting to form a twisted intramolecular charge-transfer state that is weakly emissive in nature. Quantum chemical calculations support the proposition of the bond twisting process in the photoexcited Thioflavin T and suggest that the twisting around the central C-C single bond, rather than the C-N single bond, of the Thioflavin T molecule is mainly responsible for the observed ultrafast dynamics in the excited state [110].

![Graph showing optical properties of different polymers](image-url)
Rodrigueze et al. synthesized multifunctional molecules, having both amyloid binding and metal chelating properties and reported the potential of these new multifunctional thioflavin-based chelating agents as Alzheimer's disease therapeutics [111].

**Thioflavin T - Compound Summary**

**2D Structure**

**3D Structure**

Fig.1 - 2D and 3D structures of Thioflavin T

**IUPAC Name:** 4-(3,6-dimethyl-1,3-benzothiazol-3-ium-2-yl)-N,N Dimethyl aniline

**Canonical SMILES:** CC1=CC2=C(C=C1)[N+]([=C(S2)C3=CC=CC=C(C=C3)N(C)C)C

**Pharmacological action of Thio T**

Fluorescent Dyes - Agents that emit light after excitation by light. The wavelength of the emitted light is usually longer than that of the incident light. Fluorochromes are substances that cause fluorescence in other substances, i.e., dyes used to mark or label other compounds with fluorescent tags.

Maskevich et al. reported spectral properties of thioflavin T in solvents with different dielectric properties and in a fibril-incorporated form and suggested that at phi = 90 degrees (270 degrees), the low barrier (only 700 cm-1) of the internal rotation of the benzothiazole and aminobenzene rings relative to each other gives rise to a subpopulation of Thio T molecules having a violated system of the pi-conjugated bonds of the benzothiazole and aminobenzene rings [112]. Biancalana and Koide worked on molecular mechanism of Thio -T binding to amyloid fibrils and provided important information about amyloid structure and the process of fibril formation. They provided guidance to lead further designing of new generation of amyloid [113].
Reactivity Profile of Stilbene

Trans-stilbene may react vigorously with strong oxidizing agents. It may react exothermically with reducing agents to release gaseous hydrogen.

Wess et al. found Muscarinic acetylcholine receptor M1 as a feasible target of neurological disorders like Alzheimer and Schizophrenia [114]. Muscarinic acetylcholine receptor M1 is commonly found in exocrine glands and the CNS [115-117] but mostly located in cerebral cortex and hippocampus [118,119]. Muscarinic M1 receptors play an important role in the negative regulation of cognitive processes such as learning and memory [120-123].

mGlu5 receptor antagonist

mGlu5 receptor (Metabotropic glutamate receptor 5) antagonists are widely used in peripheral and central nervous system disorders [124]. A highly selective and brain-penetrant mGlu5 receptor antagonist MPEP (2-methyl-6-(phenylethynyl)pyridine) [125-131] exhibits the therapeutic potential. Researchers suggested that mGlu5 receptor antagonists show the widest and most robust anxiolytic activity [132]. Noeska et al. used topological pharmacophore descriptor (CATS) and a self-organizing map (SOM) for forecast multiple receptor synergy of known mGluR antagonists. The tested mGlu ligand showed the calculated binding pattern for forecast target panel. The virtual screening concept provided a bottom to early identification of potential side effects of lead discovery [133]. Anxiolytic drugs of different type apply their ef-
fect through the GABA–benzodiazepine (BZD) receptor complex but peptide neurotransmitter neuropeptide Y (NPY) also generates anxiolytic effect \[^{[134-137]}\]. So, Wieronska et al made an attempt to investigate that whether MPEP (mGlu5 receptor antagonist) exerts anxiolytic effect through mechanism involving either GABA-benzodiazepine (BZD) receptor or Peptide neurotransmitter neuropeptide Y (NPY) and reported that the anxiolytic action of MPEP is carried out through NPY neurons with the participation of Y1 receptors in the amygdale. The Benzodiazepine does not contribute in this effect \[^{[138-141]}\]. A famous research drug 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine (MTEP), antagonist of metabotropic glutamate receptor was developed by Merck and Co. MTEP was discovered through structure activity relationship on MPEP \[^{[142-148]}\].

Fenobam is an atypical anxiolytic agent. The non-GABAergic activity of Fenobam is associated with its vigorous anxiolytic activity, and leads to potential development of mGlu5 receptor antagonists with an improved therapeutic novel anxiolytic agents \[^{149}\]. It blocks 66% of the mGlu5 receptor basal activity with an IC\(_{50}\) = 84 ± 13 nM. Andersen et al. have studied the mode of binding of compounds to mGlu5 receptors in brain both in vitro and in vivo by the use of \[^{[3]}\]Hmethoxymethyl-3-[(2-methyl-1,3-thiazol-4-yl)ethyl]pyridine([\(^{3}\)Hmethoxy methyl-MTEP). By the phosphoinositide hydrolysis in vivo they compare receptor occupancy with the functional efficacy of the mGlu5 antagonist \[^{150}\].

Five important neurotransmitters, involved in anxiety are Glutamate, serotonin, norepinephrine, gamma-aminobutyric acid (GABA), Corticotropin-releasing hormone (CRH) and cholecystokinin \[^{151,152}\]. Serotonin and GABA are inhibitory neurotransmitters as they tranquilize the stress response, while the rest play a part in initiating it. Selective serotonin reuptake inhibitors and benzodiazepines are most extensively recommended for treatment of these disorders.

![Fig.3 - Core structure of Benzodiazepines](image-url)
The major function of glutamate receptor is conversion of synaptic plasticity. Activation of glutamate receptor is anxiogenic function while inhibition of glutamate receptor is anxiolytic function.

![Glutamic acid](image)

Fig. 4 - Glutamic acid

Metabotropic glutamate receptor 5 (mGluR5) are mainly located at postsynaptic site and increase NMDA receptor activity and risk of excitotoxicity \[153\]. Beyond the orthostatic site as far as possible two specific allosteric binding sites are present on mGlu5 receptor \[154\]. MGlur5 may be an influential target for the treatment of anxiety and other CNS disease. Researchers are taking interest in research of selective antagonist and negative allosteric modulators of mGluR5, due to their anxiolytic, antidepressant and anti-addictive effects \[155,156\].

The introduction of MPEP (2-methyl-6-(phenylethynyl)pyridine a non-competitive mGluR5 antagonist led to perceptive of possible therapeutic application of mGluR5 antagonist in various psychiatric and neurological disorders and boost essay of some new non-competitive mGlu5 receptor antagonists \[157,158\].

![MPEP](image)

Fig. 5 - MPEP

Another research drug is MTEP (3-(2-Methyl-4-thiazolyl ethynyl) pyridine) that was developed as a selective allosteric antagonist of the metabotropic glutamate receptor, subtype mGluR5. It also acts as a lead compound in order to improve selectivity, potency and pharmacokinetics of new drugs for treatment of anxiety \[159\].
Fenobam (1-(3-chlorophenyl)-3-(3-methyl-5-oxo-4H-imidazol-2-yl)urea) is another anxiolytic drug and it is an imidazole derivative. It also acts as a potent and selective negative allosteric modulator of mGluR5. It could not commercially used due to its dose-limit in side effects \[160-162\].

Recently so many mGluR5 non-competitive antagonists has been discovered which are not topologically similar to MPEP but show good potency. Andrew S. et al. reported 6-substituted-4-anilinoquinazoline as a non-competitive antagonist of mGluR5 \[163\].

**Sedative agents**

Reduction of irritability, anxiety and stress by administration of drug is known as sedation and drug that induces sedation is known as sedative drug or tranquilizer. Generally, sedation is used in minor surgical operations and for high-anxiety subjects. The effective range of tranquilizers is used to calm down anxious people and induce sleep. Higher dose of these drugs results in hypnotic effects and can cause poor judgement ability, hypotension, airway obstruction, slow and uncertain reflexes, unconsciousness and death.

A research group have described the discovery of two novel sedative and analgesic agents (1a) and (1b) \[164\], belonging to the pyrazolo[3,4-b]pyrrolo[3,4-d]pyridine series, which displayed their CNS action as muscarinic M₁ receptor agonists \[165\]. They described the optimization of the synthetic methodology exploited to obtain the pyrazolo [3,4-b] pyrrolo[3,4-d]pyridine sedative prototype 1a and novel analogues designed by successive molecular simplifications. They showed that 1a
and the novel structurally-related analogue 1e were the most efficient compounds to impair the locomotor activity in mice at the dose of 10μmol/kg.

Barbiturates and benzodiazepines are widely used as sedative drugs. Midazolam (Versed) [166], Diazepam (Valium), Chlordiazepoxide (Librium) are most common benzodiazepines and secobarbital (Seconal) and pentobarbital (Nembutal) are example of barbiturates, used as sedative drugs. If these drugs are taken regularly in high dose for a long time, their side effects result in dependence and tolerance. Their effect and tolerance are associated with their effects on GABAergic neurotransmission in the CNS.

Fig.8 - Structures of some example of benzodiazepines and barbiturates.

Zopiclone (Pyrrolopyrazinone), Zolpidem (Imidazopyridine), Zaleplon (Pyrazolopyrimidine) are the heterocyclic sedative drugs which are the non-benzodizepine drugs and have replaced barbiturates and benzodiazepine with their fewer side effects [167,168]. These three drugs are known as “Z-drugs”. These are positive allosteric modulators of GABA_A receptors. They evoke rapid onset of action and full night’s sleep. They show affinities to benzodiazepine receptor.
Some new sedative non benzodiazepine agents, using heterocyclic compounds, have been developed with improved potency and fewer side effects. Nițulescu et al. synthesized N-(1-methyl-1H-pyrazole-4-carbonyl)-thiourea derivatives and evaluated their analgesic and sedative effects by determined them with IR and NMR analysis[169].

Najib J. reported that Eszopiclone ((S)-6-(5-Chloro-2-pyridinyl)-7-oxo- 6,7-dihydro- 5H-pyrrolo[3,4-b]pyrazin-5-yl- 4-methyl- 1-piperazinecarboxylate) is an arrogant and endured option for the treatment for sleep disorders[170]. MRK-409 binds to benzodiazepine site in human’s recombinant but due to preclinical non-sedative anxiolytic profile it could not ingeminate into humans[171]. Menegatti et al. synthesized four novel pyrazolo [3,4-b]pyrrolo [3,4-d]pyridine derivatives[172]. Ghotekar et al. synthesized novel heterocyclic compounds such as pyrazolo[3,4-b]pyrrolo[2,3-d]pyridines (PPP) from pyrazolo[3,4-b]pyridines[173]. Nascimento Jr. et al. synthesized pyrazolo[3,4-b]pyrrolo[3,4-d]pyridine derivatives and reported that pyrazolo[3,4-b]pyrrolo[3,4-d]pyridine derivatives with para-nitro substituent and para-methoxy substituent have shown highest sedative activity. Evidence suggests that pyrazolo [3,4-b]pyrrolo[3,4-d]pyridine derivatives with nitro may act as a muscarinic agonist. These results remark the influence of phenyl group bonded to the pyrazole ring of the pyrazolo [3,4-b]pyrrolo[3,4-d]pyridine derivatives in order to induce sedative activity and all the subunits present in the structure are important to promote sedative effect[174].

Antidepressant

Depression is a debilitating psychological disorder or mood disorder. People suffering from depression feel sadness, emptiness; they don’t have any interest in social or personal activity. Some bad experience of life event and side effect of some drugs or medical treatment also induce depression[175].
Hippocampus region is essential to storage of memory and according to researches hippocampus region found small in depressed person than people those are not depressed. Although it also has been proven that adult hippocampal Neurogenesis is not so useful in development of depression but may be useful for behavioural effect of antidepressants [176]. Serotonin or 5-hydroxytryptamine (5-HT) or 3-(2-aminoethyl)-1H-indol-5-ol finds in most primitive part in CNS [177]. It is responsible for control fundamental physiological aspects of the body and contributes to feel good or happiness. Serotonin deficiency causes depression. It has been proved that high cortisol level in blood increase serotonin reuptake [178]. Depletion of serotonin takes place in hypothalamus, amygdala, and cortical areas in the brain and contributes in depression.

Fig.10 - Serotonin

Selective serotonin reuptake inhibitors (SSRIs) are most popular antidepressants because they have an improved side effect profile than the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs) [179]. Serotonin reuptake inhibitors (SSRIs) block the reuptake of serotonin, which leads to increased serotonergic action and reduce depression [180-186].

The first SSRI was Zimilidine [187]. In 1974 fluoxetine and in 1986 highly selective and potent citalopram was reported. Some other SSRIs like fluvoxamine in 1983, sertraline in 1990, and paroxetine were reported in 1991.

Fig.11- Zimelidine
Some examples of antidepressant agents in common clinical use are Celexa (Citalopram)\textsuperscript{[188]}, Luvox (Fluvoxamine)\textsuperscript{[189,190]}, Paxil (Paroxetine), Pexeva (Paroxetine)\textsuperscript{[191,192]}, Prozac (Fluoxetine)\textsuperscript{[193]}, Sarafem (Fluoxetine Hydrochloride), Zoloft (Sertraline)\textsuperscript{[194,195]}, etc.

These antidepressants inhibit reuptake of serotonin and result in free serotonin released in the brain to communicate between neurons. It has been reported that if SSRIs will be given with MAO inhibitors, it will result in “Serotonin syndrome”\textsuperscript{[196,197]}. Serotonin receptors or 5-hydroxytryptamine receptors or 5-HT receptors are major target of antidepressants. Today so many 5-HT antagonists are available which belong to several chemical classes. It is not necessary that a particular class agent will bind with a particular receptor population, with some structural changes they can bind with more selectivity\textsuperscript{[198-200]}.

It has been proved that presynaptic 5-HT antagonism and postsynaptic 5-HT agonism may be favourable feature for agents to target the treatment of depression\textsuperscript{[201]}. It has been proved that 5-HT\textsubscript{1A} receptors take part in the expression of the AD properties of fluoxetine and other SSRIs\textsuperscript{[202,203]}. Alkylpiperidine spiperone is a 5-HT\textsubscript{1A} antagonist but, it shows less selectivity. Buspirone is a partial 5-HT\textsubscript{1A} agonist, used clinically for the treatment of anxiety and depression. Several benzofuran de-
derivatives linked to a 3-indoletetrahydropyridine through an alkyl chain were prepared and evaluated for serotonin transporter and 5-HT$_{1A}$ receptor affinities. Their design, synthesis and structure–activity relationships were described. Zhou D. et al. synthesized 2-Piperazin1-ylquinoline analogues and evaluated them as dual Serotonin reuptake inhibitors and serotonin 5-HT$_{1A}$ receptor antagonists. Nicol T. hatzenbuhler suggested that 3-Aminochroman derivatives show dual serotonin transporter and 5HT$_{1A}$ receptor affinity. It has been reported that Arylpiperazinyl-cyclohexyl indole derivatives also show dual 5-HT 1A receptor and serotonin transporter affinity. Sanacora et al. reported that use of selective serotonin reuptake inhibitors improve low occipital cortex GABA concentration that contribute in the treatment of depression. Wellsow et al. have investigated the quantitative structure–activity relationship of serotonin transporter ligands for the development of new radiotracers of serotonin transporters.

Zhongqi Shen et al. synthesized a series of novel lactum-fused chroman derivative. They obtained and evaluated all derivatives in racemic mixture. Out of twenty nine (29) compounds four (4) compounds were in enantiomeric form. They reported that some of five membered ring derivatives display antagonist profile. Their one enantiomer displays antagonist activity while another displays partially or fully agonist activity. This study suggested that Cyclo propylmethyl induces antagonist property of the molecule. Researchers suggested that either the differences in electronic or hydrogen bonding properties produced by moving from primary amide to secondary amide or awkward conformation inherent in the lactum group induce less potent 5-HT$_{1A}$ antagonist activity.

**GABA reuptake inhibitor**

International league against Epilepsy and International Bureau of Epilepsy reported that an epileptic seizure (convulsion) is a short-term manifestation of signs and symptoms due to irregular enormous or allochonic neuronal activity in the brain. In simple partial seizure consciousness not be affected but in complex partial seizure consciousness may be completely lost. Some time partial seizure spread to rest part of brain and look like generalized tonic-clonic seizure. Anticonvulsant drugs interact with voltage-dependent sodium channels, which are responsible to
induce action potential of nerve fibres, leading to the fast depolarization across the cell network \cite{214-216}.

The real cause of epilepsy is unknown but stroke, dementia, traumatic brain injury, Infections (brain abscess, meningitis, AIDS), congenital brain defect, brain injury, brain tumour, abnormal blood vessels in brain or other illness that damage brain tissues or uses of certain medicines specially antidepressants are common causes of epilepsy. According to report of campaign against epilepsy conducted by world health organization (WHO) around 1% of the world population is suffering from this neurological disorder \cite{217} and every year about 2.4 million new patients join these figure. Researchers have suggested that only 20–30% patients respond to currently used therapeutic agents \cite{218}. Recently, for development of innovative therapeutics so much work has been done which results in availability of some newer auspicious anticonvulsants. Example- Neurontin (gabapentin), Zonegran (Zonisamide), Trileptal (oxcarbazepine), Lamotrigine, Topiramate, Tiagabine \cite{219-222}.

![Structures of some anticonvulsants agents.](image)

These drugs are effective \cite{223,224} but they have some side effects. Therefore, there is still a requirement for new antiepileptic drugs with clinical effectiveness, tolerability and toxicity.
GABA reuptake inhibitors (GRIs) are used as anticonvulsants, as antiepileptic, as anxiolytic, as hypnotics, as muscle relaxants, and as analgesics. GRIs block the action of gamma-aminobutyric acid transporters (GATs) and lead to increase in GABAergic neurotransmission. They are also significantly used as anaesthetics in surgery. So they are widely used in neurological disorders. Some GRIs are NNC-711, SKF-89976A, Gabitril, vigabatrin (VGB) and tiagabine (TGB) [225-227].

Benzothiazole is among the usually occurred heterocyclic nuclei in many marine as well as natural plant products possessing the wide range of biological application [228-232]. Riluzole was found as an important inhibitor of GABA reuptakes that exerts its anticonvulsant and neuroprotective activity by diminished glutamate release. At high concentration it affects both uptake and release of neurotransmitters dopamine, glutamate, aspartate and GABA [233-235]. Jimonet et al. have synthesized two series of analogues of riluzole. 2-benzothiazolamines having alkyl, polyfluoroalkyl or polyfluoroalkoxy substituent in the 6-position showed potent anticonvulsant activity. 2-imino-3-(2-methylthio)- and 2-imino-3-(2-methylsulfinyl)-ethyl-6-trifluoromethoxy benzothiazolines was found as most potent derivative with ED$_{50}$ = 1.0 [236].

Chakole et al. synthesized substituted benzothiazole derivatives of thioquinazoline and reported their anticonvulsant activity [237]. Siddiqui et al. synthesized a series of sulphonamide derivatives [238] and a series of 1,3-benzothiazol-2-yl semicarbazones derivatives and reported their anticonvulsant activity against MES test [239]. Furthermore in 2009 Siddiqui et al. synthesized various N-(5-chloro-6-substituted-benzothiazol-2-yl)-N’-(substitutedphenyl)-[1,3,4]thiadiazole-2,5-diamine derivatives and screened them for their anticonvulsant activity against MES induced seizure [240]. Mohd. Amir et al. synthesized a series of N-(6-chlorobenzothiazol-2-yl)-2-substituted-acetamides$\&$N-(6-chlorobenzothiazol-2-yl)-2-(substituted-benzyldene) hydrazine carbothioamide and reported anticonvulsant activity of derivatives [241]. Furthermore N-(substituted benzothiazol-2-yl) amide derivatives were synthesized by Hassan et al. and have been evaluated for their anticonvulsant and neuroprotective effect. N-(6-methoxybenzothiazol-2-yl)-4-oxo-4-phenylbutanamide was reported as most effective anticonvulsant compound median doses of 40.96 mg/kg [242]. 6-bromo-2-ethyl-3-(substituted benzo[d]thiazol-2-yl)quinazolin-4(3H)-one were synthesized and evaluated for anticonvulsant activity by Ugale et al. 3-(benzo[d]thiazol-
2-yl)-6-bromo-2-ethylquinazolin-4(3H)-one & 6-bromo-2-ethyl-3-(6-methoxybenzo[d]thiazol-2-yl)quinazolin-4(3H)-one have shown most anticonvulsant activity \(^{[243]}\). Siddiqui N. reported synthesized series of 3,4-disubstituted benzaldehyde-\(N\)-(6-substituted-1,3-benzo[d]thiazol-2-yl)semicarbazones derivatives and evaluated their anticonvulsant activity by using the maximal electroshock seizure (MES) method. \(^{[244]}\) Kumar P. et al. designed and synthesized a series of 2-(2-substituted hydrazinyl)-1,3-benzo[d]thiazole and 2-(1,3-benzo[d]thiazole-2-ylsulphanyl)-\(N'\)- (substituted) acetohydrazide and evaluated anticonvulsant activity and neurotoxicity \(^{[245]}\). Navale et al. synthesized a series of substituted benzo[d]thiazol-2-ylcarbamates and evaluated for anticonvulsant activity PTZ-induced convulsion and maximal electroshock models \(^{[246]}\).

Amnerkar N.D. and Bhusari K.P. synthesized a series of 6-substituted-[3-substituted-prop-2-eneamido]benzothiazole and 6-substituted-2-[(1-acetyl-5-substituted)-2-pyrazolin-3-yl] aminobenzothiazole derivatives and figured out their neurotoxicity, hepatotoxicity and behavioural study \(^{[247]}\).

Zheng et al. synthesized twenty novel \(N\)-diarylalkenyl-piperidinecarboxylic acid derivatives and reported \((R)-1-[4,4\text{-bis}(3\text{-phenoxymethyl}-2\text{-thienyl})-3\text{-butenyl}]\)3-piperidinecarboxylic hydrochloride as most potent GABA uptake inhibitor \(^{[248]}\). Altomare et al. reported QSAR study for the serum catalyzed hydrolysis of a series of X-phenyl esters of nipeptic acid and discussed result in respect of design of ester prodrugs of polar GABA-mimetics and other CNS-active compounds \(^{[249]}\). Trapani et al. studied structure-activity relationships (SAR) of series of alkylphenols and p-X-substituted congeners proved that p-iodo-2,6-diisopropylphenol displayed anticonvulsant and anticonflict effects \(^{[250]}\). Tiagabine also found as potentially effective in the treatment of chronic seizure disorder \(^{[251-253]}\). Johnston et al. studied different isoxazole, Nipecotic acid and other related compounds and found 4,5,6,7-tetrahydroisoxazo[4,5-\(\epsilon\)]pyridin-3-ol derivative as most potent GABA uptake inhibitor \(^{[254]}\). Mizoule et al. worked on 2-Amino-6-trifluoromethoxy benzothiazole (PK 26124) and found that it prevents convulsions induced by maximal electroshock, inhibitors of the \(\gamma\)-aminobutyric acid (GABA) formation and ouabain, it has antagonistic properties of excitatory dicarboxylic amino acids and which help in its anticonvulsion action \(^{[255]}\). Johnston et al. reported that compounds containing substitut-
ents 2-fluoro, 3-hydroxy and 2-amino show more affinities for the uptake mechanism than GABA. P-chloromercuriphenylsulphonate, N-ethylmaleimide, chlorpromazine and haloperidol potentially inhibited $[^3]$H GABA. $[^3]$H GABA uptake was also tested in homogenates of cerebral cortex and other parts of central nervous system. Kinetic property of rapid uptake of $[^3]$H GABA and inhibitor sensitivity was found similar in slices of intact tissue and particles when homogenates were incubated with amino acids $^{[256]}$.

Molecular structures data (drawn by software ACD/CHEMSKETCH FREE VERSION) $^{[257]}$ and descriptors (calculated by Pclient software) $^{[258]}$ ported into SARCHITECT Designer $^{[259]}$. Support vector machines are atypical class of supervised learning methods which is commonly used based on kernel functions to apply linear classification techniques to non-linear classification problems $^{[260]}$. There are different types of support vector machines- Linear, Polynomial and sigmoid etc. Support vectors machines execute classification by create a hyperplane that optimally distribute data into two categories. In SVM method predictor variables are known as attributes and transformed attributes, used to define hyperplane are known as features. A feature that elucidates one case (row of predictor values) is known as vector. By SVM modelling we found the optimal hyperplane that distributed clusters of vector in such a manner that cases with one category of the target variable are on one side of the plane and cases with the other category are on the other side of the plane. The vectors closed the hyperplane are known as the support vectors. SVM show non-linear relationship of molecular descriptors with binding affinity of compounds by using non-linear kernel function.

Parameters used in support vector machine-

**Kernel Type** - Some common kernels are polynomial (homogeneous), radial basis function, Gaussian radial basis function and sigmoid. Interweaved data set can be divided by Polynomial kernel and Gaussian kernels. Herein, Gaussian kernel function was used in forward selection wrapper with epsilon value 0.1 (the acceptable difference between the target value for regression and the calculated value). Maximum number of repetition- high number of repetition can improve synchronism. Default number of repetition is set as 100.
Cost value - It is a forfeit of misclassification. Cost value 100 is used as default value. If this parameters increase, it will reduce the training error at the cost of generalization achieved by the regression model. Increasing cost value results in totally different separating plane with more support vectors and fewer misclassifications.

Ratio - The ratio of cost of misclassification of one category to the cost of misclassification of other category is set as 1. Changing in ratio will cost forfeit misclassification for one category more than for the other category. By setting of ratio we can control number of false negative and increase number of false positive.

Sigma value - It is parameter of Gaussian kernel. Default value of sigma is set as 1.0. If optimum value of sigma is low than this value, it will decrease misclassification (training error) and generalization and going above this value increases misclassification. Optimum value of sigma should be near to the average nearest acquaintance distance. SVM regression method was used to build Models by using Gaussian kernel function to predict non-linear relationship between activity and descriptors.

Molecular Descriptors

Out of thousands of molecular descriptors investigated till now, only few of them are used to exhibit QSAR in the present work. The selection of molecular descriptor is performed by support vector machines. The different types of molecular descriptor belonging to main categories may be summarized followed with distinguished use/uses in the different chapters of the proposed work.

1. Getaway descriptors

   HATS4p-Leverage-weighted autocorrelation of lag 4 / weighted by polarizability (Chapter -3)

   H4e-H autocorrelation of lag 4 weighted by atomic Sanderson electronegativity (Chapter -6)

   R6u-R autocorrelation of lag 6 unweighted (Chapter-4)

   HTm-H total index weighted by atomic (Chapter-7) (For Multiple Linear Regression)
2. Geometric descriptor

- \( G(O..O) \)-Sum of geometrical distances between O..O \((\text{Chapter-3})\)
- \( \text{PJI3} \)-3D Petitjean shape index \((\text{Chapter-5})\)

3. RDF descriptor

- \( \text{RDF030u} \)-Radial Distribution Function - 030 / unweighted \((\text{Chapter-3})\)
- \( \text{RDF090v} \)-Radial Distribution Function - 9 weighted by atomic van der Waals volumes \((\text{Chapter-4})\)

4. Surface area descriptors

- \( \text{TPSA (N…O)} \)-Topological polar surface area using N, O polar contributions \((\text{Chapter-3})\)
- \( \text{FHAccVSA} \)-Fractional van der Waals surface area of hydrogen bond acceptors \((\text{Chapter-7})\) (For SVM aided \text{Non-Linear} regression)

5. E-state indices

- \( \text{SeaC2N3aa} \)-Molecular Bond E-state indices \((\text{Chapter-3})\)

6. 3-D Morse descriptors

- \( \text{Mor15u} \)-signal 15 unweighted \((\text{Chapter-6})\)
- \( \text{Mor15e} \)-signal 15 weighted by atomic Sanderson electronegativities \((\text{Chapter-6})\)
- \( \text{Mor18m} \)-signal 18 weighted by atomic mass \((\text{Chapter-4})\)
- \( \text{Mor29e} \)-signal 29 weighted by atomic Sanderson electronegativities \((\text{Chapter-5})\)
- \( \text{Mor02e} \)-signal 2 weighted by atomic Sanderson electronegativities \((\text{Chapter-7})\) (For Multiple \text{Linear} Regression)

7. WHIM Descriptor

- \( \text{G1e} \)-1\(^{\text{st}}\) component symmetry directional WHIM index / weighted by atomic Sanderson electronegativities \((\text{Chapter-6})\)
- \( \text{E3e} \)-3rd component accessibility directional WHIM index weighted by atomic Sanderson electronegativities \((\text{Chapter-4})\)
8. 2D Autocorrelation Descriptors

GATS4e - Geary autocorrelation - lag 4 weighted by atomic Sanderson electronegativities (Chapter-5)

MATS5m - Moran autocorrelation - lag 5 weighted by atomic (Chapter-7)
(For Multiple Linear Regression)

GATS2p-Geary autocorrelation-lag 2 weighted by atomic polarizability (Chapter-7) (For SVM aided Non-Linear regression)

9. Constitutional descriptors

nCp- No. of total primary Carbons (sp3) (Functional group count) (Chapter-7)
(For Multiple Linear Regression)

R-CR-R- Atom centred fragment (Chapter-7) (For SVM aided Non-Linear regression)

10. Topological 2D descriptor

BEHm4-Highest eigenvalue n. 4 of Burden matrix weighted by atomic masses (Chapter-7) (For SVM aided Non-Linear regression)

11. Topological Charge indices

JGI7-Mean topological charge index of order 7 (Chapter-7) (For Multiple Linear Regression)

JGI9-Mean topological charge index of order9 (Chapter-7) (For SVM aided Non-Linear regression).

1. GETAWAY descriptors

The Getaway (Geometry, Topology, and Atom-Weights Assembly) descriptors are molecular descriptors derived from the Molecular Influence Matrix (MIM). Four types of Getaway descriptors are computed in Sarchitect, HATSkw, Hkw, Rkw and R+kw, where $1 \leq k \leq 8$, and $w \in (u,m,e,v,p)^{261}$.

HATS descriptors are computed on a Hydrogen-filled molecule. The molecular influence matrix $H$ is constructed as follows.
Let $M$ be the geometric distance matrix having $n$ rows and 3 columns, one row for each of the $n$ atoms present in the molecule and one column for each of the Cartesian coordinates of the atoms in the molecule. The atomic coordinates are assumed to be calculated with respect to the geometric centre of the molecule. The Molecular Influence matrix $H$ is obtained from $M$ as:

$$H = M \cdot (MT \cdot M)^{-1} \cdot MT,$$

Where, $MT$ is the transpose of $M$ and $(MT \cdot M)^{-1}$ is the inverse of $(MT \cdot M)$.

Each of the HATS descriptors is of the form $HATSkw$ where $1 \leq k \leq 8$ and $\omega \in \{m, p, e, v\}$ Let the atoms $i$ and $j$ be separated by a lag $k$ as in other autocorrelation descriptors. Let $h_{ii}$ and $h_{ij}$ be the diagonal entries corresponding to the atoms $i$ and $j$ in the $H$ Matrix. Then:

$$HATSkw = \sum_{i=1}^{n} \sum_{j=1}^{n} (w_i h_{ii}) (w_j h_{ij}) \delta(k, d_{ij}),$$

$\delta(k; D_{ij})$ is Kronecker delta, i.e. $\delta(k; d_{ij}) = 1$ if the $ij^{th}$ entry in the Topological Level Matrix is $= k$, and $\delta(k; d_{ij}) = 0$ otherwise.

$Hkw$ is defined as:

$$Hkw = \sum_{i=1}^{n} \sum_{j=1}^{n} (h_{ij} w_i w_j) \delta(k, d_{ij}; h_{ij}).$$

2. Geometric descriptors

Geometric descriptors characterize the shape and extent of the molecule in terms of its 3-D coordinates. As a result accurate coordinates are required and so the structure must be geometry optimized before these descriptors can be calculated \[262-264\]. Examples include moment of inertia, molecular surface area and volumes and shadow descriptors the surface area and volume descriptors are usually used in combination with atomic properties and are useful in characterizing the distribution of these properties. The drawback to these descriptors is that they require accurate molecular geometries and thus for large sets of molecules the optimization step can become time consuming.

Path/Walk Shape Indices

The Atomic path/Walk Index for the $ith$ atom is the ratio between Atomic Path Count and Atomic walk Count of same length $m$; $m = 2,3,4,5$. The Molecular Path/Walk Index is defined as the average sum of atomic path/walk indices of equal length \[265\].
The shape descriptor, *Petitjean Shape index* $I_2$ (PJI2) is a topological anisometry descriptor. It is defined as:

$$I_2 = (D - R)/R$$

### 3. RDF descriptor

The radial distribution function (RDF) of an ensemble of $n$ atoms can be interpreted as the probability distribution of finding an atom in a spherical volume of radius $R$. A typical RDF descriptor is denoted by $RDF_{sw}$ where $1.0 \leq s \leq 15.5$ in units of 0.5 and the weights may be some property associated with the atoms such as $m$ (relative atomic mass), $p$ (polarizability), $e$ (Sanderson electronegativity) or $v$ (Van der Waals volume) [266-267].

$$RDF (R, w) = f \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} w_i w_j e^{-\beta(R-rij)^2}$$

Where, $f$ is a scaling factor, $rij$ is the Euclidean distance between the atoms $i$ and $j$, $w_i$ and $w_j$ are the weights of the atoms $i$ and $j$ respectively, $n$ is the total number of atoms, $\beta$ is the smoothing parameter which defines the probability distribution of the individual inter-atomic distance. $\beta$ can be interpreted as the temperature factor that defines the movement of the atoms.

### 4. Surface area descriptors

Three types of surfaces which can be defined for a molecule:

**Van der Waals Surface** of a molecule is the outer envelope (that separates atoms from the surroundings) of the union of van der Waals surfaces of the atoms in the molecule.

**Solvent Accessible Surface** of a molecule is the outer envelope of the union of solvent accessible surfaces of atoms in the molecule. The solvent accessible surface of an atom is the surface of a sphere whose radius is the sum of the Van der Waals radius of that atom and the radius of the solvent molecules. **Molecular Surface** of a molecule is the envelope of the molecule that remains after a spherical eraser is used to wipe out the exterior space wherever possible. What remains after this operation is the portion of the space occupied by the Van der Waal spheres that represent the atoms in the molecule, and the space in the wedge between the atoms.
that are not reachable by the eraser. Sarchitect computes the surface Area of a molecule using the following method. For each atom, we define the Van der Waals sphere centred at the centre of the atom and radius being the corresponding Van der Waals radius. The Van der Waals Surface of a molecule is the outer envelope of the Van der Waals spheres of the atoms. Since the Van der Waals spheres of atoms overlap, only a portion of the Van der Waals sphere of each atom contributes to the Van der Waals Surface Area of a molecule. The molecule is sliced along a chosen axis and the contribution of each of the atoms in that slice to the total surface area is computed. The surface area for each atom is summed over the slices to compute the surface area of each atom, and these are summed to compute the total surface area of the molecule. Various surface area descriptors can be computed by property-based partitioning of the surface area.

5. E-state Indices

The E-state program calculates atom-type and bond-type E-state indices. Five groups of indices are calculated. Each group of indices is represented by a single index in E-state indices group. In fact all of them are index groups with variable number of indices. Each index has a name that depends on atom or bond type and value [268-270].

(i) E-state atom type indices

Basic set of indices consists of electrotopological state indices proposed by Hall and Kier.

(ii) E-state extended atom type indices

A set of extended indices for O and N atoms was also developed to take into account their functional groups and neighborhood. The name of an extended index consisted of the name of original E-state index and name extension that depended on the atom neighborhood. All nitrogen atoms were divided into five groups. These groups include aliphatic (extension "(al)") and aromatic amines ("(ar)"), salts of amines ("(salt)"), nitrogens of nitro and nitroso groups ("(nitro)"), and other types of nitrogen ("oth"). In the same way oxygen atoms of OH groups (sOH E-state index) were classified as atoms of alcohols ("(alc)"), phenols ("(phen)"), carboxylic acids ("(acid)"), amino acids ("(zwit)"). Among the atoms of
double-bonded oxygen (dO E-state index) the atoms of ketones ("(keto)"), carboxylic
acids ("(acid)"), esters ("(ester)"), amides ("(amid)"), nitro and nitroso groups ("(nitro)"), sulfones and sulfoxides ("(sulfo)"") were distinguished.

(iii) **E-state bond indices.**

The bond-type E-state indices are used to describe two atom states. Firstly, an intrinsic state value is assigned to each edge and then the perturbation from each other edge was computed and added to the analyzed edge value. The bond E-state value was then computed as

\[ I_{ij} = (I_i + I_j)/2 , BES_{ij} = I_{ij} + I_{ij}/(r_{ij}^2 + 1)^2 \]

Where, \( r_{ij} \) is computed as the average \( r_{ij} \) for the atoms in the two bonds. These values were computed for individual bonds and then were collected for each type of the bond in the molecule. Names of the bond type electrotopological state indices are different from those proposed by Hall and Kier, although they are basically the same. These names also start with bond order indicator (e1, e2, e3 and ea for single, double, triple and aromatic bonds respectively) and are followed by two atom type names. Atom type names include atom name and the number of skeletal bonds for that atom. Finally an indication of the unused bonds of each atom is given. The unused bonds are always mentioned in our implementation. This makes it different from original version by Kier and Hall where an indication of unused bonds is given "if necessary".

6. **3-D Morse descriptors**

3D MoRSE descriptors (3D Molecule Representation of Structures based on Electron diffraction) are derived from infrared spectra simulations using a generalized scattering function. A typical MoRSE descriptor is denoted by \( Morsw \) where \( s \) and \( w \) take the values \( 1 \leq s \leq 32 \) and as before \[271-275]\.

\[ Mors(s,w) = I(s,w) = \sum \sum_{j=2}^{s-1} w_i w_j \sin(sr_{ij})/(sr_{ij}), \]

where, \( rij \) is the Euclidean distance between the atoms \( i \) and \( j \), and \( wi \) and \( wj \) are the weights of the atoms \( i \) and \( j \) respectively.
7. Whim descriptor

WHIM descriptors are based on statistical indices calculated on the projections of atoms along principal axes\textsuperscript{1276-279}. They are built in such a way as to capture relevant 3D molecular information regarding the molecular size, shape, and symmetry and atom distribution with respect to invariant Reference frames. The descriptors are computed by Principal Components Analysis on the centred Cartesian coordinates of a molecule by using a weighted covariance matrix obtained from different weighing schemes for the atoms. The weighted covariance matrix is a 3x3 matrix whose elements are the weighted covariance $S_{jk}$ between $j^{th}$ and $k^{th}$ atomic coordinates for $j,k \in (1,2,3)$ defined as:

\[
S_{jk}^w = \sum_{i=1}^{n} \gamma_i (q_{ij} - \overline{q}_j)(q_{ik} - \overline{q}_k) / \sum_{i=1}^{n} \gamma_i
\]

Where, $n$ is the number of atoms, $w_i$ is the weight of the $i^{th}$ atom, $q_{ij}$ and $q_{ik}$ are the $j^{th}$ and the $k^{th}$ coordinates of the $i^{th}$ atom and $w_i$ the weight of the $i^{th}$ atom is one of the six weighting schemes defined above.

8. 2D Autocorrelation Descriptors

The autocorrelation descriptors available in Sarchitect are: Broto-Moreau Autocorrelation Descriptors (ATS), Moran Autocorrelation Descriptors (MATS) and Geary Autocorrelation Descriptors (GATS). The symbol for each of the autocorrelation descriptors is followed by two indices $d$ and $w$ where $d$ stands for the lag and $w$ stands for the weight. For instance, ATS4m means the Broto-Moreau Autocorrelation Descriptor of lag 4 that is weighted by mass. The lag is defined as the topological distance $d$ between pairs of atoms. The topological distance between a pair of atoms $(i,j)$ is given in the $ij^{th}$ entry in the Topological Level Matrix. The lag can have a value between 0 and 8. The weight can be $m$ (relative atomic mass), $p$ (polarizability), $e$ (Sanderson electronegativities) and $v$ (Van der Waals volume). Relative mass is defined as the ratio of atomic mass of an atom to that of carbon. Similarly, the other three weights $p$, $e$ and $v$ are scaled by the corresponding values for Carbon. Let $n$ be the number of atoms in the molecule. For any chosen value for lag $d$ and any chosen weight $w$, the Autocorrelation Descriptors are computed as described below. Broto-Moreau Autocorrelation Descriptors \textsuperscript{280-284}
\[ A TS_{\omega \psi} = \sum_{i=1}^{n} \sum_{j=1}^{n} \delta_{ij}(w_i, w_j), \]

Where, \( w_i \) and \( w_j \) are the weights of the atoms \( i \) and \( j \), \( \omega \in \{ m, p, e, v \} \), and \( \delta_{ij} \) is the Kronecker delta, i.e. \( \delta_{ij} = 1 \) if the \( ijth \) entry in the Topological Level Matrix is \( d \), and \( \delta_{ij} = 0 \) otherwise.

9. Constitutional Descriptor

(i) Functional group count

Constitutional descriptors are the most simple and commonly used descriptors, reflecting the chemical composition of a compound without any information about its molecular geometry or atom connectivity.\(^{[285]}\). Constitutional descriptors can be well explained by their definition such as the molecular weight (MW), number of atoms (nAT), number of Hydrogen atoms (nH), number of Carbon atoms (nC), number of Nitrogen atoms (nN), number of Oxygen atoms (nO), number of halogen atoms (nX). The number of rotatable bonds (RBN) is the number of bonds which allow free rotation around themselves. These are defined as any single bond, not in a ring, bound to a non terminal heavy atom. Excluded from the count are amide C–N bonds because of their high rotational energy barrier.

\[
\begin{align*}
\text{RBN} = 2 & \quad \text{RBN} = 1 & \quad \text{RBN} = 1 & \quad \text{RBN} = 2 & \quad \text{RBN} = 0
\end{align*}
\]

The number of rings (nCIC) counts the rings in a molecule. The number of rings (or independent cycles, i.e., the number of non-overlapping cycles) in a graph is commonly known as the cyclomatic number. The number of rings (nCIC) is calculated as the cardinality of the set of independent rings called the Smallest Set of Smallest Rings (SSSR). The number of donor atoms for H-bonds (nHDon) is a measure of the hydrogen-bonding ability of a molecule expressed in terms of number of possible hydrogen-bond donors. Specifically, it is calculated by adding up the hydrogen bonded to any nitrogen and oxygen without negative charge in the molecule.
The number of acceptor atoms for H-bonds (nHAcc) is a measure of the hydrogen-bonding ability of a molecule expressed in terms of number of possible hydrogen-bond acceptors. Specifically, it is calculated by adding up any nitrogen, oxygen and fluorine, excluding N with positive formal charge, higher oxidation states and pyrrolyl form of nitrogen.

(ii) Atom centred fragment

Atom centred fragment descriptors define each ring atom that has three neighbours. The typical formats are A-BC- -D, A-B(=C)-D and A-BC where the atom C on a ring is viewed as the centre with A and D being its ring neighbours and B (that is not on the same ring as A, C and D) is connected to B. The atoms A, C and D can be Hydrogen (represented as H), Carbons (represented as R) and heteroatoms (represented as X). '-', '=', and '#' stand for single, aromatic, double and triple bonds respectively. For example, R-CH-R can be defined as a central Carbon atom (C) on an aromatic ring that has two carbon neighbours (R) on the same aromatic ring and the third neighbour outside this ring is a Hydrogen (H).

10. Topological 2D descriptor

The BCUT (Burden - CAS - University of Texas Eigen values) descriptors are the eigen values of a modified connectivity matrix known as the Burden matrix \[^{286-289} \]. The Burden matrices \( M \) are defined such that: The diagonal elements \( M_{ww} \) are the weights \( W_i \) for atom \( A_i \) where the weights may be some property associated with the atoms such as \( m \) (relative atomic mass), \( p \) (polarizability), \( e \) (Sanderson electronegativity) or \( v \) (Van der Waals volume). Relative mass is defined as the ratio of atomic mass of an atom to that of carbon. Similarly, the other three weights \( p, e \) and \( v \) are scaled by the corresponding values for Carbon. The non-diagonal elements \( M_{wk} \) are 1 if \( k = dij \) and 0 otherwise, where \( k \) is the lag - defined as the topological distance \( d \) between the atom pair \( ij \) and may have a value between 0-8. Thus for a given \( k \), the non-diagonal element \( M_{ij} \) will be unity if the atoms \( i \) and \( j \) are apart by a topological distance \( k \) and zero otherwise. For a given \( w \) and \( k \), there are two BCUT descriptors \( BEH_{wk} \) and \( BEL_{wk} \): \( BEH_{wk} \) is the highest positive Eigen value of the matrix \( M_{wk} \) and will be zero if there are no positive eigen values. \( BEL_{wk} \) is the low-
est negative Eigen value of the matrix $M_{wk}$ and zero if there are no negative eigenvalues.

11. Topological Charge indices

The Topological Charge Indices evaluate the charge transfer between pairs of atoms and hence the global charge transfers in the molecule. They are computed using the Topological Level Matrix, Reciprocal Square Distance Matrix and the Adjacency Matrix defined below. The Topological Level Matrix contains the topological distance between a pair of atoms $i$ and $j$ as its $ij^{th}$ entry $^{[290-293]}$. The Reciprocal Square Distance Matrix $D^{-2}$ is defined as the square matrix in which the $ith$ entry $= 1/d_{ij}^2$ if $i \neq j$ and 0 otherwise, where $d_{ij}$ is the $ij^{th}$ entry in the topological level matrix. The Adjacency Matrix is defined as the square matrix in which the $ij^{th}$ entry is 1 if $i$ and $j$ are connected by a bond and 0 otherwise. The Galvez Matrix $M$ is defined as:

$$M = A.D^{-2}$$

The vertex degree $\delta_i$ of an atom $i$ is defined as the number of atoms adjacent to it in the H-depleted molecular graph. The Charge Term Matrix $CT$ is defined as:

$$CT_{ij} = \delta_i$$ if $i = j$

Where, $\delta_i$ is the vertex degree of the $ith$ atom. The diagonal entries in the matrix are the vertex degrees of the corresponding atom, and the non-diagonal entries are $CT_{ij}=m_{ij} - m_{ji}$ and $m_{ij}$ are the elements of the Galvez matrix $M$. The Topological Charge Index $GG_k$ is defined as:

$$\mathcal{G}_k = \frac{1}{2} \sum_{i=1}^{n} \sum_{j \neq i} |CT_{ij}| \delta(k; d_{ij})$$

Where, $n$ is the total number of non-Hydrogen atoms in the molecule, $\delta(k; d_{ij}) = 1$, if $d_{ij} = k$ and 0 otherwise. The Mean Topological Charge Index $JG_k$ is defined as:

$$\mathcal{J}_k = GG_k / (n-1)$$

Survey of literature has shown that till date no attempt is made for modelling, monitoring and estimating the biological activity of the CNS acting drugs using proposed molecular descriptors.
Every possible sincere effort has been made to provide the citation for the literature which has referred.
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