Chapter 2

LITERATURE REVIEW
Nayak et al. (2015) synthesized various pyrazoline carboxylates from ethyl 2-benzylidene-3-oxobutanoate ester using hydrazine hydrate and ethanol as solvent. For all the compounds, the activity for MAO inhibition was studied with the help of rat brain MAO. The competitive, selective and reversible MAO-B inhibitors activity was found for all the synthesized compounds. At concentration close to 1µM, most of the synthesized compounds behaved as MAO-B inhibitors.

![Chemical Structure](image)

Where R= 2-NO2, 2-Cl, 2-OCH3, 2-CH3, H
R1= H, 4-OCH3, 4-CH3, 4-Cl, 4- NO2

A series of novel inhibitors of MAOs, 2H-chromene-3-carboxamide derivatives, were synthesized by Pan et al. (2014) and evaluated for their MAO inhibitory activity for both isoforms. The synthesized compounds showed promise for their higher selectivity towards MAO-B isoform. The probable binding model of the potential compounds was determined by performing the docking calculations into the active site of the complex structure of hMAO-B. From the results it was concluded that the hydrogen bond interaction was involved between conserved CYSA 172 residue and ligand, and Pi-Pi interaction was found between the benzene-ring of the active compound and residue ILEA199. The conserved residue CYSA172 played a very important role for binding of the ligand.

![Chemical Structure](image)

Xu He et al. (2014) synthesized coumarin derivatives and tested them against monoamine oxidase A and B. The steric effect was analysed for both isoform by posing and scoring behaviour of the binding interactions. The potential compound was docked with hMAO-B complex, which showed that the conserved residue ILE 199 had great importance for ligand binding and the Sigma–Pi interaction was found between ligand and residue ILE199.
From the seeds of *Achyranthes aspera*, a biologically potent flavonoid compound was isolated by Beula *et al.* (2014), and its molecular interaction was established towards monoamine oxidase-A enzyme. The isolated flavonoid was structurally ascertained by UV, $^1$H NMR, $^{13}$C NMR, DEPT 90, DEPT 135 and ESI-MS. Molecular level interaction was studied through molecular docking simulation. The 5,7-dihydroxy-2-(4-hydroxyphenyl)-6-(3-methylbut-2-en-1-yl)-4H-chromen-4-one was isolated by chromatographic techniques. It was noticed that the isolated flavonoid possessed potent monoamine oxidase-A inhibition, with a docking score of −8.06 and calculated inhibition constant of about 1.23 µM. By performing molecular docking studies, they proposed that the isolated flavonoid could successfully dock into the inhibitor-binding pocket of human monoamine oxidase-A isoform with appreciable predicted affinity. Therefore it was concluded that the 6-prenyl apigenin could be a valid scaffold for designing novel monoamine oxidase-A inhibitors.

Mertens *et al.* (2014) synthesized alkynyl–coumarinyl ethers via hydroxyl coumarins, whose phenolic group at position 6, 7 or 8 was converted by means of the Mitsunobu reaction, and tested their hMAO-B inhibitory activity. At the fused benzene ring, the position of the alkynyloxy chain and the residue at 3-position of the pyran-2H-one part played a major role to optimize the inhibitory activity. They found that the 7-position of hex-5-ynyloxy chain showed particular advantageous effect. The three methoxycarbonyl derivative was act as dual inhibitors towards MAO-A and MAO-B, and strong anti-MAO-B potency was shown by the 3-(4-methoxy)phenyl derivative.
Synthesis of $\alpha$-tetralone (3,4-dihydro-2H-naphthalen-1-one) derivatives was done by Legoabe et al. (2014) as recombinant h-MAO A and B inhibitors. The $\alpha$-tetralones were found as most active MAO-B inhibitors. The highly active compound, 6-(3-iodobenzyloxy)-3,4-dihydro-2H-naphthalen-1-one, exhibited 287-fold selectivity for MAO-B over the MAO-A isoform, while the other most active inhibitor, 6-(3-cyanobenzyloxy)-3,4-dihydro-2H-naphthalen-1-one, exhibited 3.25-fold selectivity towards MAO-A. On the C6 position of the $\alpha$-tetralone moiety, benzyloxy, phenylethoxy and phenylpropoxy substitutions were more favourable for MAO-A inhibition. On the meta and para positions of the benzyloxy ring, the presence of halogen and alkyl substituents, enhanced the h-MAO-B inhibitory potentials. The results concluded that the synthesized derivatives of $\alpha$-tetralone were promising candidates for the design of therapies for depression and Parkinson’s disease.

Aksoz et al. (2014) synthesized 2-pyrazoline and a series of hydrazone derivatives and tested their inhibitory activity toward hMAO. All compounds reversibly and competitively inhibited both isoforms of hMAO (MAO-A or MAO-B), except one compound, which showed selective MAO-B inhibition. They performed the computational study by docking the tested compounds into the active site of the h-MAOs isozymes.

Gol et al. (2014) synthesized pyrazoline with hydrazine hydrate, which cyclised the substituted chalcones in the presence of acidic and basic conditions. They performed the comparative study between conventional heating and microwave irradiation on the basis of percentage yields. Microwave irradiation accelerated all the reactions in the presence of acidic and basic conditions with higher yields. The characterization of the synthesized compounds was done by spectral study (IR, MS, $^1$H and $^{13}$C NMR) and
they were evaluated for their antifungal and antibacterial activity. Some compounds exhibited prominent activity against *S. aureus, E. faecalis, E. coli, S. typhi, C. albicans* and *M. luteus*.

![Chemical structures](image)

The high concentration of MAO-B as an appropriate and prospective tracer target for molecular imaging biomarkers are the basis for early AD detection, and due to this reason Neudorfer *et al.* (2014) decided to develop a compound library of selective and reversible MAO-B inhibitors. They modified the core structure of 3-(anthracen-9-yl)-5-phenyl-4,5-dihydro-1H-pyrazolesbiosisternically. The synthesized pyrazoline based derivatives, which may be the precursor substance for the future radiolabelling along with reference compounds for the investigation of increased MAO-B levels in AD.

![Chemical structure](image)

Sun *et al.* (2013) designed hybrids of tacrine–homoisoflavonoid and studied them as cholinesterase (ChEs) inhibitors and h-MAOs inhibitors. The potency of the potent compounds was found against the enzyme MAO-B and ChEs. A six carbon linker between tacrine and (E)-7-hydroxy-3-(4 methoxybenzylidene)chroman-4-one, was most potent against AChE and MAO-B. By membrane permeation (artificial) assay, the synthesized compound was observed to cross the BBB. They concluded that the hybrids compound, with a 6 carbon linker between tacrine and (E)-7-hydroxy-3-(4 methoxybenzylidene)chroman-4-one was an excellent multifunctional promising compound for designing of novel drugs for Alzheimers disease (AD).
An attempt was made by Robinson et al. (2013) to search the inhibitory MAO potential of substituted heterocyclics and their effect on the versatile chalcone scaffold. They synthesized a furanochalcone series and these furan substituted phenylpropenones exhibited good inhibitory activities towards MAO-B, but were inactive toward the MAO-A enzyme. The highly active compound, 2E-3-(5-chlorofuran-2-yl)-1-(3-chlorophenyl)prop-2-en-1-one; showed reversible inhibition. The competitive mode of binding was revealed by kinetic analysis.

Chimenti et al. (2013) reported the 4-substituted-2-thiazolylhydrazone derivatives and evaluated them in vitro for their hMAO-A and B inhibitory activity. The substitution of thiazole ring at C4 position generated highly active and selective hMAO-B inhibitors, with nanomolar values. Moreover, the reversible mechanism for the inhibition of enzyme was endowed to these compounds. To rationalize the recognition of all inhibitors with respect to hMAO-A and -B isoforms, the molecular modelling studies were performed.

A group of (2E,4E)-1-(2-hydroxyphenyl)-5-phenylpenta-2,4-dien-1-ones and (2Z,4E)-3-hydroxy-1-(2-hydroxyphenyl)-5-phenylpenta-2,4-dien-1-ones were
synthesized, by Desideri et al. (2013), and evaluated in vitro against both isoforms of human monoamine oxidase (hMAO), MAO-A and MAO-B. The reactive compounds showed selective inhibitory activity against MAO-B in micromolar range. The most potent hMAO-B inhibitors, (2E,4E)-5-(4-Chlorophenyl)-1-(2-hydroxy-4-methoxyphenyl)penta-2,4-dien-1-one and (2E,4E)-5-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)penta-2,4-dien-1-one, were coupled with high selectivity. The MAO inhibitory recognition of the highly active compounds was elucidated by the quantum chemistry and molecular mechanics methods.

Matos et al. (2013) synthesized (coumarin-3-yl) carbamates active against monoamine oxidase enzyme. The micro or nanomolar ranges of the active compounds showed the selective inhibition of MAO-B isoenzyme, as compared with that of selegiline. The evaluation of ADME properties, in vivo assays and docking calculations were also carried out for the compound benzyl (coumarin-3-yl) carbamate.

Meiring et al. (2013) prepared 3, 4-dihydro-2(1H)-quinolinone derivatives and studied their inhibitory activity for recombinant hMAO A and B. The 3, 4-dihydro-2(1H)-quinolinone derivatives were structurally similar to the reported derivatives of coumarin (1-benzopyran-2-one), tested as MAO-B inhibitors. The 7-(3-bromobenzyloxy)-3, 4-dihydro-2(1H)-quinolinone, was found as most the active MAO-B inhibitor. The 3,4-dihydro-2(1H)-quinolinone derivative was substituted with benzyloxy substituent on the C7 position which lead to significantly more potent inhibition compared to substitution on C6. It was the most potential candidate for the parkinson’s disease therapy.
Pisani et al. (2013) investigated the alteration in the physicochemical properties such as shape, size, lipophilicity, H bonding, etc. that affect MAOs inhibition potential on C4 substitution of substituted 2H-chromen-2-one derivatives. The 67 compounds synthesized showed great selectivity against MAO-B; some of them had good potency in the nanomolar range. In this range, 7-metachlorobenzyloxy-4-oxyacetamido-2H-chromen-2-one showed high selectivity towards MAO-B over the isoform MAO-A. The models were generated by docking studies with some selected compounds, with special attention to the dominant role of the steric effects. They found some interesting results that many of the designed substituents could be metabolically related to each other (e.g., CH$_3$/CH$_2$OH/CHO/COOH; NH$_2$/NHCH$_3$, NHAc), and the obtained results may contribute in predicting the in vivo activity of putative metabolites of lead MAO-B inhibitors.

![Chemical structure](image)

Park et al. (2013) reported the derivatives of thiazolopyridine and oxazolopyridine as MAO-B inhibitors. The oxazolopyridine core structure was the best choice for piperidino group and the R1 amino substituent as was revealed by the structure–activity relationship study. The activities of the phenyl rings with the oxazolopyridines had IC$_{50}$ values between 267.1 and 889.5 nM. The basic structure was interestingly replaced from oxazolopyrine to thiazolopyridine, and significantly improved activities were found with the thiazolopyridine core structure. The van der Waals interactions in the human MAO-B active site were studied by molecular docking, which explained the enhanced inhibitory activities of thiazolopyridine derivatives.

![Chemical structure](image)

Jo et al. (2013) identified the pharmacophores exhibiting great activities against MAO-A and MAO-B, by utilizing the structure–activity relationship studies. The several chromenyl chalcones were accordingly designed for the inhibitory effects of the
synthesized compounds as for of MAO-B enzyme, which was determined by using an MAO-B enzyme assay kit and HPLC. (E)-3-(6-Methoxy-2Hchromen-3-yl)-1-(2-methoxyphenyl)prop-2-en-1-one exhibited a half-maximal inhibitory concentration of 320 nM. The *in silico* docking studies were performed to elucidate its molecular-level binding mode with the three-dimensional structure of MAO-B.

Polyamine derivatives of $N^1,N^{12}$ dibenzyldodecane-1,12- diamine and $N^1$-benzyl-spermine (BD6), were proposed by Bonaiuto *et al.* (2013) and was used as vascular-adhesion-protein -1 (VAP-1) and “probes” (potential substrates or inhibitors) of h-MAO A and MAO B. The most effective compound of this group worked as a competitive MAO B inhibitor and as an irreversible MAO-A inhibitor. The thiophene ring containing asymmetric spermine analogue showed a reversible mixed inhibition, selective for MAO-B. They performed docking studies and found the various binding poses of most active compound into the active site cavities of the two MAO isoforms which explained the various mode of inhibition of the most active compound. The $\varepsilon$ amino group of Lys 305 of MAO A was found as a possible target for the ITC group of the inhibitor.

A novel compound of tacrine selegiline hybrid was synthesised by Lu *et al.* (2013) as cholinesterase (AChE/BuChE) inhibitor and monoamine oxidase (MAO-A/B) inhibitor. The results indicated that the inhibitory activity was reinforced by most of the synthesized compounds. Among these compounds, potent compound provided a good amount of activity towards AChE, Bu ChE, MAO-A and MAO-B, and the $IC_{50}$ values of all targets were 22.6 nM, 9.37 nM, 0.3724 mM, and 0.1810 mM respectively. The conclusion was derived that for Alzheimer’s disease the active compound had the potential as a multi-functional candidate.
Strydom et al. (2013) studied the phthalide [2-benzofuran-1(3H)-one] derivatives as MAO inhibitors. They demonstrated that the substitution at C6 of the phthalide moiety, yielded compounds with high binding affinities to both human MAO isoforms. In most cases, MAO-B specific inhibition was exhibited by C6-substituted phthalides. The general order of potency was CF3 > I > Br > Cl > F > CH3 > H, exhibited among the derivatives of 6-benzylxyophthalides having substituents on the para position of the phenyl ring. They concluded that the substituted phthalides, at C-6 position may act as lead precursor for the treatment of neurodegenerative disorders such as Parkinson’s disease.

Nayak et al. (2013) reported pyrazoline derivatives of phenyl and ethyl carbamate as inhibitors of MAO isoforms. All the active compounds showed the inhibitory activity selectively towards MAO-A. A great selectivity index was displayed by the phenyl carbamate derivatives as compared to ethyl carbamate derivatives. Compound 3-(2-Hydroxy-phenyl)-5-p-tolyl-4,5-dihydro-pyrazole-1-carboxylic acid phenyl ester was equally potent as the standard drug, moclobemide, with a good selectivity index (8.86 × 10^−5).

Helguera et al. (2013) predicted the inhibitory potential of human MAO by rationally designed and developed quantitative structure activity relationships. Firstly, an
appropriate dataset of heterocyclic compounds was selected that included coumarins, chromones, chalcones and thiazolylhydrazones, etc, then are liable QSAR models built-up by applying linear discriminant analysis to the data derived from different molecular representations. Then, the feature selection algorithms were applied by which the selectivity and inhibitory activity toward human MAO could be predicted. They also reported that several QSAR models could be combined to make better predictions.

Okaecwe et al. (2012) reported studies of 8-benzyloxycaffeine series as reversible and most active inhibitors of isoforms of human MAO-A and -B. An additional caffeine derivative was discovered by them as an potent MAO inhibitor. The MAO inhibitory action of 8-phenoxyethylcaffeine and 8-[(phenylsulfanyl)methyl] caffeine were tested and the obtained results were documented. The 8-phenoxyethylcaffeine derivatives showed potent reversible inhibition of MAO-B, while the 8-(phenylsulfanyl) methyl caffeine derivatives acted as weak MAO-B inhibitors. They derived the conclusion that the 8-phenoxyethylcaffeines could behave as useful leads compound for the selective MAO-B inhibitors. Such compounds can play a potential role in the treatment of neurodegenerative disorders, as Parkinson’s disease. Using molecular docking, they also proposed possible binding orientations of selected caffeine derivatives in the active sites of MAO-A and -B.

Secci et al. (2012) synthesized substituted pyrazolines derivatives as dual inhibitors towards different classes of enzymes (cyclooxygenase, acetyl cholinesterase, butyrylcholinesterase) synergistically. Due to the direct correlation with the potential MAO inhibition, the synthesized compounds displayed the activities of antidepressant and anticonvulsant in animal models.
Havrylyuk et al. (2012) studied 3-[2-(3,5-diaeryl-4,5-dihydropyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-ylidene]-2,3-dihydro-1H-indol-2-ones and 3-(3,5-diaerylpyrazol-1-yl)-2,3-dihydro-1H-indol-2-ones as antitumor agents. Most of the active compounds showed anticancer activity on melanoma, leukaemia, lung, colon, CNS, ovarian, prostate, renal, and breast cancers cell lines. The highly active anticancer compounds had the mean of GI50 and TGI values of 0.071 µM and 0.76 µM, respectively.

Novel compounds of 3-aryl-4-hydroxycoumarin were synthesized by Serra et al. (2012) as selective MAO-B inhibitors. The inhibitory activities of the synthesized derivatives were influenced by the substitution of chloro and methoxy groups, in the meta and para positions respectively of the 3-phenyl ring. Moreover, in the sixth position of the moiety, the presence of a chloro atom enhanced the inhibition and selectivity against MAO-B, as compared with the reference compound iproniazide. The most reactive preferred orientations adopted by the active compounds inside the MAO-B binding pocket could be understood by docking studies.

Mishra et al. (2012) reported some pyrazolines as selective and reversible MAO-B inhibitors. Amongst them, the most reactive analog selectively inhibited the MAO-B activity in liver and brain. On acute administration of potent derivative, no alteration was observed in amine levels, whereas, the significant increase in striatal dopamine level was noticed on its chronic administration. It also potentiated the 2-phenylethylamine induced stereotype behaviour, the reserpine induced glutathione
oxidation (in cerebrum), partially reversed the reserpine induced oral dyskinesia, was protected by it and no hypertensive crisis was observed on tyramine co-treatment. An effort was made by Mishra et al. (2011) to develop selective MAO B inhibitors. An in-house library was made using structure based virtual screening and all the derivatives were found to be selective, reversible and active in nM range towards MAO-B, and were found to be 100 times more potent than selegiline.

Jagrat et al. (2011) reported twenty-two pyrazoline derivatives and tested them for their hMAOinhibitory activity. Twelve molecules, with substituted ring C and unsubstituted ring A, were found as active inhibitors of hMAO-A isoform with SIMAO-A. The presence of ring C increased the potency as well as selectivity index (SI) towards hMAO-A.

Ten novel 3, 5- diaryl pyrazolines were synthesized by Sahoo et al. (2010) which showed inhibitory monoamine oxidase (MAO) activity. The active compounds possessed reversible and selective inhibition for MAOs isoforms (MAO-A or MAO-B). Further, the evaluation of the possible interactions between the derivatives and monoamine oxidases (MAO-A/MAO-B) was theoretically aided by the docking studies.
N1-thiocarbamoyl-3, 5-di (hetero) aryl-4, 5-dihydro-(1H)-pyrazole derivatives were proposed by Chimenti et al. (2010) and tested for their ability to inhibit the activity of the isoforms of human monoamine oxidase (hMAO) A and B. Some of the synthesized compounds contained a selective inhibitory activity against hMAO-B in the micromolar range.

N-substituted-3-[(20-hydroxy-40-prenyloxy)-phenyl]-5-phenyl-4,5-dihydro-(1H)-pyrazolines were synthesized by Fioravanti et al. (2010) and tested on human monoamine oxidase-A and B isoforms. Molecular modeling and structure–activity relationships explained that the substitutions, such as chlorine or benzyloxy, improved the interaction with active site of hMAO-B.

Some substituted 3-aryl- 4, 5-dihydropyrazoles-1-carbothioamides were synthesized by Maccioni et al. (2010). Regardless of the substitution on the heterocyclic ring, they had activity towards the selective MAO-B isoform of the enzyme. Docking studies were performed with the aim to rationalize the mechanism of inhibition of the most potent and selective compound.

Karuppasamy et al. (2010) prepared some 3, 5-diaryl pyrazoline analogs. The active compounds showed the selective and reversible inhibition towards MAO-A with SI in the magnitude of 103–105.
Kaplancıklı et al. (2010) designed triazolo-pyrazoline derivatives and tested their potential for antidepressant activity. In the test series compounds, different levels of antidepressant activities were exhibited when compared to reference drug, fluoxetine.

Gong et al. (2010) reported 1, 3, 5-triaryl pyrazoline derivatives, prepared with the help of chalcones and 3-chloro-6-hydrazinylpyridazine with 47–82% yields. The groups attached to the benzene rings influenced the absorption maxima of the compounds, which differed from 332 to 342 nm. The groups present in the benzene ring also affected the emission spectra of compounds. Methoxy group acted as a strong electron-donating group in benzene ring on C3 position of pyrazoline and made the emission wavelength of red shift, than that by compounds with chlorine group. The fluorescence and absorption intensity was also correlated with the substituents on the two aryl rings. In addition, with increasing solvent polarity the absorption spectra of these compounds changed very little.

3-aryl-4,5-dihydropyrazoles-1-carbothioamide compounds have been studied by Maccioni et al. (2010). Regardless of the substitution on the heterocyclic ring of the active compound, the selective activity was found towards the MAO-B isoform of the enzyme. The mechanism of inhibition of the most active and selective compound was rationalized with the help of docking experiments.

Combined pharmacophore and structure based modelling approach was used by Boppana et al. (2009) to understand the monoamine oxidase B interaction with known ligands. The docking results explained that the docking models and pharmacophore
were in good agreement. Docking studies were performed, subsequently on the cluster representatives of 530 hits from 5500 compounds. They were used to identify the selective MAO-B inhibitors.

Kelekçi et al. (2009) synthesized a pyrazoline series from a quinazolinone ring and tested them for anxiogenic, antidepressant and MAOs inhibitory activities by *in-vivo* and *in-vitro* tests, respectively. Most of the potential compounds possessed high activity against both, isoforms of MAOs (MAO-A and MAO-B).

Chimenti et al. (2008) synthesized a series of N1-propanoyl-3, 5-diphenyl-4,5-dihydro-(1H)-pyrazole derivatives and assayed their MAO-A and MAO-B inhibitory activity. To a great extent, the potential compounds showed inhibitory activity toward MAO-A selectively, with micromolar values. In addition, most selective compound further went through computational studies to highlight the most relevant interactions in the mechanism of recognition within both, the MAO-A and the MAO-B enzyme active sites.

The synthesis of twelve 3-(2-thienyl) pyrazoline derivatives was described by Ozdemir et al. (2008) and tested them as anticonvulsant and antidepressant. All the synthesized compounds were structurally confirmed by IR, UV, 1H-NMR, mass spectral data and microanalyses. None of the derivative showed neurotoxicity at 30–300 mg/kg dose levels.

Where Ar: C₆H₅, 2-thienyl and R: CH₃, C₂H₅, C₃H₅, C₆H₅
Ozdemir et al. (2007) synthesized twelve 1-phenyl-, 1-thiocarbamoyl- and 1-N-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazoline derivatives and tested them for their antidepressant and anticonvulsant activities. 1,5-Diphenyl-3-(2-furyl)-2-pyrazoline, 1-N-allylthiocarbamoyl-3-(2-furyl)-5-phenyl-2-pyrazoline, 1-N-allylthiocarbamoyl-3, 5-di(2-furyl)-2-pyrazoline and 1-N-phenylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline were active at 100-300 mg kg\(^{-1}\) dose levels. 1-Thiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline, 1-N-methylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline and 1-N-ethylthiocarbamoyl-3, 5-di(2-furyl)-2-pyrazoline were found to be protective against scMet and MES at 30-300 mg kg\(^{-1}\) dose levels.

Kelekçi et al. (2007) synthesized 1-thiocarbamoyl-3-substituted phenyl-5-(2-pyrrolyl)-4,5-dihydro-(1H)-pyrazole derivatives as MAO-B inhibitors. Most of the potential compounds were found to be highly active against both, the MAO-A and the MAO-B, isoforms.

Edmondson et al. (2007) explained the catalytic mechanism of pharmacologically important, membrane bound flavoenzymes (MAO-A and MAO-B) via, two different ways; the single electron transfer and the polar nucleophilic mechanisms. This has attracted numerous investigations due to their versatile pharmacological importance.

Ruhoglu et al. (2005) synthesized 1-phenyl-, 1-thiocarbamoyland 1-N-substituted thiocarbamoyl 1-3-phenyl-5-heteroaryl-2-pyrazoline derivatives as antidepressant and anticonvulsant. The spectral and microanalysis confirmed the chemical structures of the synthesized compounds.
Rajendra Prasad et al. (2005) synthesized five new 1, 3, 5-triphenyl-2-pyrazoline and another five new 3-(2''-hydroxy naphthalen-1''-yl)-1, 5-diphenyl-2 pyrazolines. The electron-donating groups, such as dimethyl amino, hydroxyl and methoxy substituents, found on both the aromatic rings at positions 3 and 5 of pyrazolines derivatives, significantly enhanced the antidepressant activity when considered with the pyrazolines having no substituents on the phenyl rings.

N. Gokhan et al. (2003) reported the pyrazoline derivatives of 1-N-substituted thiocarbamoyl-3-phenyl-5-thienyl-2-pyrazolines as MAO inhibitors.

Chimenti et al. (2002) synthesized 1-acetyl-3, 5-diphenyl-4, 5-dihydro-(1H)-pyrazole derivatives and investigated them for their potential to inhibit bovine serum amine oxidase, selectively monoamine oxidases and swine kidney oxidase. The reported compounds act as reversible and non-competitive inhibitors for all types of the assayed amine oxidases. In particular, 1-acetyl-3-(2, 4-dihydroxyphenyl)-5-(3-methylphenyl)-4, 5-dihydro-(1H)-pyrazole acted as a potent monoamine oxidase inhibitor.

Palaska et al. (2001) reported new 3, 5-diphenyl-2- pyrazoline derivatives obtained by treating 1, 3-diphenyl-2-propen-1-one with hydrazine hydrate. 3-(4-Methoxyphenyl)-5-(3,4-dimethoxyphenyl)-2 pyrazoline 3-(4-methoxyphenyl)-5-(2-chloro-3, 4-dimethoxyphenyl)-2- pyrazoline and 3-(4-chlorophenyl)-5-(2-chloro-3, 4-
dimethoxyphenyl)-2- pyrazoline. The 4-methoxy and 4-chloro substituents, at 3-
position on the phenyl ring of the pyrazoline, increased the antidepressant activity. The
replacement of these groups by bromo and methyl substituents decreased the
antidepressant activity in mice.

Palaska et al. (1996) synthesized ten 1, 3, 5-triphenyl-2-pyrazoline derivatives by
treating 1,3-diphenyl-2-propen-1-one with phenyl hydrazine. 1-Phenyl-3-(4-
methylphenyl)-5-(3,4-dimethoxyphenyl)-2-pyrazoline and 1-phenyl-3-(4-
methylphenyl)-5-(2-chloro-3,4-dimethoxyphenyl)-2- pyrazoline were developed as
antidepressant. On the phenyl ring at 3-position of the pyrazoline ring, a methyl
substituent increased the antidepressant activity.

Rose et al. (1989) studied the application of 1-methyl-4-phenyl-1, 2, 3, 6-
tetrahydropyridine (MPTP) to common marmosets induced motor deficits; associated
with a marked decrease in the uptake of $[^3$H] dopamine into synaptosomes in the
putamen. The concentration of dopamine reduced in both caudate nucleus and
nucleus accumbens and in the zona compacta of the substantia nigra, appropriate loss
of dopamine was observed and in the ventral tegmental area loss was noticed by
histological studies. The transient depletion of dopamine in the nucleus accumbens
and the neurotoxic effects of MPTP in the substantia nigro both were prevented by
selective inhibition of MAO-B.

The monoamine oxidase (MAO) inhibitors may show a high degree of selectivity
toward various MAO forms or toward the enzyme in specific tissues or cells, as was
studied by Fuller et al. (1978). Their selectivity may be further enhanced by the
selective inhibitor combination with amines or amine precursors or other drugs.
RESEARCH ENVISAGED

Literature survey revealed that amongst nitrogen containing five member heterocycles, pyrazolines have proved to be the most useful framework for biological activity and biodynamic behavior, with diverse chemical reactivity. The research activity in this field was stimulated by the findings of considerable biological activities by the numerous pyrazoline derivatives. They have various prominent effects, such as antimycobacterial, antimicrobial, antifungal, antiamoebic, antimalarial, anti-inflammatory, analgesic, antidepressant, anti-HIV and anticancer activities. They also have some potent receptor selective biological activity like cannabinoid CB1 receptor antagonist, monoamine oxidase (MAO) inhibitor and Nitric oxide synthase (NOS) inhibitor. Modern drug discovery starts with the identification of a pharmacologically target that is hypothetically the prime cause of disease. In modern drug development, the discovery of the pyrazoline class of drugs has led to an appreciable increase and has also mention of the unpredictability of biological activity which arise from the structural modification of a prototype drug molecule.  

A vast range of MAO inhibitors, that include reversible and irreversible, selective and non-selective inhibitors of MAO-A/ MAO-B, are now available. These are proving to have great applicability in pharmacy due to specific chemical reactivity, having therapeutic value in several diverse conditions, including affective disorders, neurodegenerative diseases, stroke, ageing, depression and anxiety. The aim of the study was focused on the introduction of chemical diversity in the molecular framework in order to synthesize pharmacologically interesting pyrazoline derivatives. It was decided to synthesize some novel 1, 3, 5 trisubstituted-2-pyrazoline derivatives for better understanding of the structure requirements, for both selectivity and inhibition, towards both MAO isoforms (MAO-A/ MAO-B). In particular, the influence, on the biological behavior due to the introduction of different aromatic rings at 1st, 3rd and 5th position of the pyrazoline nucleus shall be the aim of the study, which would be further corroborated with the computational studies.
PART 1: Synthesis:

\[
R-\text{CHO} + R'-\text{C}=\text{O} \quad \text{EtOH, NaOH} \quad 0^\circ \text{C}, \text{Stir for 2-4 hr.} \quad R-\text{CH} = \text{CH}-C-R' \quad \text{Chalcone}
\]

Aldehyde \quad \text{ketone}

\[
R-\text{CH}=\text{CH}-C-R' \quad \text{Reflux for 1-3 hrs.} \quad \text{NH}_2\text{NH}_2 /H_2O \quad R'\text{NH} \quad \text{Substituted pyrazoline}
\]

\[
\text{Substituted Pyrazoline} \quad \text{THF, Stir for 0.5-4 hrs.} \quad \text{Substituted Benzene Sulfonyl Chloride} \quad R'\text{N}\text{N}R'' \quad 1,3,5-\text{Trisubstituted} \quad -2\text{-pyrazoline}
\]

Where, \( R = \)

\[
\begin{align*}
\text{CH}_3, & \quad \text{OH}, & \quad \text{OCH}_3, \\
\end{align*}
\]

\[
\begin{align*}
R' = & \quad \text{N}, & \quad \text{OH}, & \quad \text{OCH}_3, \\
\end{align*}
\]

\[
\begin{align*}
R'' = & \quad -\text{SO}_2\cdot\text{C}_6\text{H}_4\cdot\text{COCH}_3, & \quad -\text{SO}_2\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2, & \quad -\text{H}
\end{align*}
\]
PART 2: Purification and Characterization

**Purification:**
- Recrystallization.
- Column chromatography.

**Characterization:**
- **Physical analysis**
  - Solubility.
  - Melting range.
  - Rf value.
  - Elemental analysis.
- **Spectral Analysis:**
  - I.R. Spectroscopy
  - Mass Spectroscopy
  - NMR Spectroscopy

**Part 3:** Biological evaluation

**Part 4:** Toxicity studies (of most active derivatives)