Introduction

Amine Oxidases (AOs) are the enzymes, which are responsible for the oxidative deamination of mono, di, tri and more than three units containing amines. There are two categories of AO’s that are differentiated by the cofactors present in them: one contains Flavin Adenine Dinucleotide (FAD) and the other contains copper. Copper containing AO creates a disulphide-linkage to form homodimer whereas FAD containing AO [1-2] is an oxidoreductase enzyme that contains 8α-S-cysteinyl covalently linked with FAD as redox cofactor in the outer mitochondrial membrane of neuronal, glial and peripheral regions [3-6]. The catalytic pathway for free radical formation by MAO is shown in Figure 1 [7-9]. The monoamine oxidase family members share structural features, including a conserved FAD-binding domain and a lysine-water-flavin triad. The substrate-binding sites, however, reflect the different substrates. In each case, there is evidence that the deprotonated amine is the functional substrate. While, nucleophilic and radical mechanisms have been proposed for oxidation of amines by MAO, the accumulation of structural and mechanistic evidence supports a common hydride transfer mechanism for all members of the MAO family.

MAO (Mitochondrial Monoamine Oxidases) exists in two types of isoforms MAO-A and MAO-B [10]. The amino acid sequences of both the forms are 70% identical or homologous [11]. They contain the pentapeptide sequence Ser-Gly-Gly-Cys-Tyr which binds to the FAD cofactor covalently in both the isoforms [12,13].

MAO-B is more abundant in brain as compared to MAO-A, which is present mainly in the peripheral regions such as intestine [14]. Therefore, MAO-A is mainly involved in the breakdown of amino acids like tyramine and hence its inhibition lead to an increased levels of tyrosine and other indirect sympathomimetic amines in the systemic circulation, releasing nor-adrenaline that leads to chase reaction as shown in Figure 2 [15-16].

Figure 1: Catalytic pathway for free radical formation by MAO enzyme.
There are several known reversible and irreversible MAO inhibitors as shown in Table 1 [17, 18].

### Structure to activity relationship

This review focuses on the Structure-Activity Relationship (SAR) studies of substituted thiazolyl hydrazones as MAO-A and MAO-B inhibitors, which are present in chronological order to demonstrate sequential progress in this area (Figure 3).

### Table 1: Some important reversible and irreversible MAO inhibitors.

| Structure | Name         | Selectivity |
|-----------|--------------|-------------|
|           | MAO reversible inhibitors |       |
|           | Toloxatone [17(a)] | MAO-A       |
|           | Lazabemide [17(b)] | MAO-B       |
|           | Safinamide [17(c)] | MAO-B       |
|           | Moclobemide [17(d)] | MAO-A       |
|           | MAO irreversible inhibitors |       |
|           | Clorgyline [17(e)] | MAO-A       |
|           | L-Deprenyl (selegiline) [17(f)] | MAO-B       |
|           | Pargyline [17(f)] | MAO-B       |

### Table 2: Structure and MAO-A and MAO-B inhibitory activity of 2-methylcyclohexylidene-(4-arylthiazol-2-yl) hydrazones 1-9.

| CA | R       | IC$_{50}$ (μM) | Selectivity Ratio |
|----|---------|----------------|-------------------|
|    |         | hMAO-A | hMAO-B |                |
| 1  | H       | 41.23±3.96 | 0.711±0.037 | 58               |
| 2  | 4-Cl    | 35.22±1.81 | 13.12±0.51  | 2.7              |
| 3  | 4-F     | 43.55±3.61 | 0.203±0.008 | 2.7              |
| 4  | 2,4-Cl  | 44.70±5.23 | 26.81±2.74  | 1.7              |
| 5  | 2,4-F   | 37.95±3.41 | 0.014±0.000 | 1.7              |
| 6  | 4-CH$_3$ | c       | 0.014±0.009 | >701d             |
| 7  | 4-OCH$_3$ | 2.76±0.17 | 2.37±0.14  | 1.2              |
| 8  | 4-NO$_2$ | c       | 0.032±0.002 | >3693             |
| 9  | 4-CN    | 31.03±2.44 | 0.026±0.001 | 1183             |

>Each IC$_{50}$ value is the mean ± SEM from five experiments (n=5).

>level of statistical significance: P < 0.01 versus the corresponding IC$_{50}$ values obtained against hMAO-B, as determined by ANOVA/Dunnett’s test.

>Values obtained under the assumption that the corresponding the compounds IC$_{50}$ against hMAO-A is the highest concentration tested (100 μM).

>inactive at 100 μM (highest concentration tested), at higher concentration the compounds precipitate.
In order to further explore optimum substitution patterns, a majority of substituted thiazolyl-hydrazone analogs were prepared and evaluated as MAO inhibitor in the presence of kynuramine as a substrate.

A new series of 2-Methyl Cyclohexylidene (4-arylthiazolyl-2-yl) Hydrazones (compound 1-9) have been synthesized by introducing the chiral cyclohexylidene moiety for their ability to inhibit the activity of human MAO-A and MOA-B.

In humans, MAO-B inhibitors are used in the management of Parkinson’s and Alzheimer disease, while MAO-An inhibitors are proved to be antidepressant and anxiolytic agents. Preliminary SAR studies revealed that racemic analogues 1-9 (Table 2) are selective as well as biological active for both isoenzymes hMAO-A and hMAO-B.

On basis of the molecular modelling study, the new scaffold of thiazole hydrazones are designed by doing the substitution on fourth and fifth position of the thiazole ring to make a (4,5-disubstituted-thiazole-2-yl) hydrazones which exhibit good selectivity and biological activity. Detailed description is shown in Table 3, [19-21].

Some of the substituted thiazolyl hydrazones were synthesised and evaluated for MAO Inhibitory activity (Figure 4). In this series substitution was done on C4 position of the thiazole ring by various electron withdrawing and releasing groups [22] (Table 4).

A new series of [4-(3-methoxyphenyl)-thiazol-2-yl] hydrazine derivatives were synthesized and screened for their MAO inhibitory activity. The detailed description is shown in Table 5.

Halogenated series shows interesting activity and great selectivity towards the hMAO-B as expressed in baculo virus infected insect cells (BTI-TN-5B1-4). The importance of water molecules in the binding site was also evaluated as it plays an important role in mediating the protein-ligand interactions. The entire series of the synthesized compounds were inactive towards MAO-A below 100µM, suggesting (Arylidene-2-(4-(4-Halophenyl Thiazol-2-yl Hydrazine) as a promising candidate scaffold for the design of selective MAO-B inhibitors. The substitution of the phenyl moiety at position 2 of thiazole modulates the activity within a series [22] Table 6.

A new series of 4-Substituted-2-(2-(1-(Pyridin-4-yl) ethylidene) hydrazinyl) thiazole was synthesized and evaluated for MAO inhibitory activity. In the series, only six compounds were found to be most active but all these have less activity towards the hMAO-A enzyme [22-23]. It was concluded that compounds have affinity for both isoforms Table 7.

### Table 3: Structure as well as MAO-A & MAO-B inhibitory activity of (4, 5-aliphatic disubstituted-thiazol-2-yl) hydrazones 10-27.

| CA | R   | R₁ | R₂ | R₃ | IC₅₀ (µM) | Ratio  |
|----|-----|----|----|----|----------|--------|
|    | CH₃ | CH₃ | Phenyl | CH₃ | 2.55±0.17 | 2.08   |
| 11 | CH₃ | CH₃ | Phenyl | CH₃ | 1.55±0.07 | 1.00   |
| 12 | CH₃ | (CH₂)₂CH₂ | Phenyl | CH₃ | 2.52±0.13 | 0.95   |
| 13 | CH₃ | CH₂CH | Phenyl | CH₃ | 1.65 ± 0.09 | 1.49   |
| 14 | CH₃ | CH₂CH(CH₂)₂ | Phenyl | CH₃ | 2.4 ± 0.13 | 2.78 ± 0.12 | 1.16 |
| 15 | CH₃ | CH₂CH₂CH=CH₂ | Phenyl | CH₃ | 6.97±0.43 | 8.85±0.45 | 1.27 |
| 16 | CH₃ | (CH₂)₂CH₂ | Phenyl | CH₃ | 3.69±0.11 | 6.0±2.1 | 1.64 |
| 17 | CH₃ | (CH₂)₂CH₂ | Phenyl | CH₃ | 4.13±0.22 | 4.78±0.17 | 1.16 |
| 18 | CH₂CH₂ | (CH₂)₂CH₂ | Phenyl | CH₃ | 3.91±0.19 | 3.75±0.12 | 1.04 |
| 19 | CH₂ | CH₂ | Napthalen-2-yl | H | 1.56±0.07 | 3.55±0.29 | 2.27 |
| 20 | CH₂ | CH₂CH₂ | Napthalen-2-yl | H | 1.74±0.08 | 2.65±0.19 | 1.52 |
| 21 | CH₂ | (CH₂)₂CH₂ | Napthalen-2-yl | H | 1.81±0.07 | 3.11±0.16 | 1.72 |
| 22 | CH₂CH₂ | CH₂CH₂ | Napthalen-2-yl | H | 1.86±0.06 | 2.32±0.03 | 1.25 |
| 23 | CH₂ | CH₂CH₂(CH₂)₃ | Napthalen-2-yl | H | 2.31±0.16 | 3.56±0.06 | 1.54 |
| 24 | CH₂ | CH₂CH₂(CH₂)₃ | Napthalen-2-yl | H | 1.37±0.08 | 3.94±0.25 | 2.86 |
| 25 | CH₂ | (CH₂)₂CH₂ | Napthalen-2-yl | H | 2.45±0.12 | 15.96±0.45 | 6.67 |
| 26 | CH₂ | (CH₂)₂CH₂ | Napthalen-2-yl | H | 2.93±0.12 | 3.76±0.13 | 1.28 |
| 27 | CH₂ | (CH₂)₂CH₂ | Napthalen-2-yl | H | 15.48±0.99 | D | <0.25 |

### Table 4: IC₅₀ values of Thiazolyl Hydrazones as Monoamine Oxidase Inhibitors: An Overview.

| Group | IC₅₀ (µM) | Ratio |
|-------|----------|-------|
| hMAO-A | hMAO-B | |
| CA | R   | R₁ | R₂ | R₃ | hMAO-A | hMAO-B | Ratio  |
| 10 | CH₃ | CH₃ | Phenyl | CH₃ | 2.55±0.17 | 5.28±0.36 | 2.08   |
| 11 | CH₃ | CH₃ | Phenyl | CH₃ | 1.55±0.07 | 1.53±0.21 | 1.00   |
| 12 | CH₃ | (CH₂)₂CH₂ | Phenyl | CH₃ | 2.52±0.13 | 2.31±0.08 | 0.95   |
| 13 | CH₃ | CH₂CH | Phenyl | CH₃ | 1.65 ± 0.09 | 2.45 ± 0.14 | 1.49   |
| 14 | CH₃ | CH₂CH(CH₂)₂ | Phenyl | CH₃ | 2.4 ± 0.13 | 2.78 ± 0.12 | 1.16   |
| 15 | CH₃ | CH₂CH₂CH=CH₂ | Phenyl | CH₃ | 6.97±0.43 | 8.85±0.45 | 1.27   |
| 16 | CH₃ | (CH₂)₂CH₂ | Phenyl | CH₃ | 3.69±0.11 | 6.0±2.1 | 1.64   |
| 17 | CH₃ | (CH₂)₂CH₂ | Phenyl | CH₃ | 4.13±0.22 | 4.78±0.17 | 1.16   |
| 18 | CH₂CH₂ | (CH₂)₂CH₂ | Phenyl | CH₃ | 3.91±0.19 | 3.75±0.12 | 1.04   |
| 19 | CH₂ | CH₂ | Napthalen-2-yl | H | 1.56±0.07 | 3.55±0.29 | 2.27   |
| 20 | CH₂ | CH₂CH₂ | Napthalen-2-yl | H | 1.74±0.08 | 2.65±0.19 | 1.52   |
| 21 | CH₂ | (CH₂)₂CH₂ | Napthalen-2-yl | H | 1.81±0.07 | 3.11±0.16 | 1.72   |
| 22 | CH₂CH₂ | CH₂CH₂ | Napthalen-2-yl | H | 1.86±0.06 | 2.32±0.03 | 1.25   |
| 23 | CH₂ | CH₂CH₂(CH₂)₃ | Napthalen-2-yl | H | 2.31±0.16 | 3.56±0.06 | 1.54   |
| 24 | CH₂ | CH₂CH₂(CH₂)₃ | Napthalen-2-yl | H | 1.37±0.08 | 3.94±0.25 | 2.86   |
| 25 | CH₂ | (CH₂)₂CH₂ | Napthalen-2-yl | H | 2.45±0.12 | 15.96±0.45 | 6.67   |
| 26 | CH₂ | (CH₂)₂CH₂ | Napthalen-2-yl | H | 2.93±0.12 | 3.76±0.13 | 1.28   |
| 27 | CH₂ | (CH₂)₂CH₂ | Napthalen-2-yl | H | 15.48±0.99 | D | <0.25   |

Citation: Yagyesh K, Fatima SN and Kapil K. Synthesis and Structure Activity Relationship of Thiazolyl Hydrazones as Monoamine Oxidase Inhibitors: An Overview. SM Anal Bioanal Technique. 2018; 3(1): 1015s2.
Table 4: Structure as well as MAO-A and MAO-B inhibitory activity of (4-aryl-thiazol-2-yl) hydrazones 28-40.

![Structure of (4-aryl-thiazol-2-yl) hydrazones](image)

| CA | R | R₁ | IC₅₀ (µM) | Selectivity ratio hMAO-A/hMAO-B |
|----|---|----|-----------|---------------------------------|
| 28 | Cyclopentyl | H | 7883±91¹ | 296±7                            |
| 29 | Cyclopentyl | 4-Cl | 7160±64⁰ | 262±8                            |
| 30 | Cyclopentyl | 4-F | 4443±21² | 40±0.9                           |
| 31 | Cyclopentyl | 2, 4-Cl | 54,507±142³ | 284±11                          |
| 32 | Cyclopentyl | 4-NO₂ | 344±22² | 94±3                             |
| 33 | Cyclopentyl | 4-CN | 644±21² | 221±2                            |
| 34 | Cyclohexyl | H | 48,351±143⁴ | 116±5                          |
| 35 | Cyclohexyl | 4-Cl | 2911±17¹ | 211±7                            |
| 36 | Cyclohexyl | 4-F | 1752±21¹ | 4±0.2                            |
| 37 | Cyclohexyl | 2, 4-Cl | N.E | 202±16                          |
| 38 | Cyclohexyl | 2, 4-F | 4575±143⁵ | 652±22                          |
| 39 | Cyclohexyl | 4-CH₃ | 23371±32⁴ | 3689±353                         |
| 40 | Cyclohexyl | 4-OCH₃ | 7509±21³ | 11956±131                        |

¹p<0.01 or ²p<0.01 versus the corresponding IC₅₀ values obtained against hMAO-B, as determined by ANOVA/Dunnett's. N.E=inactive at 100 µM (highest concentration tested). ³Value obtained under the assumption that the corresponding IC₅₀ against hMAO-A is the highest concentration tested (100 µM).

Figure 4: SAR of (4-aryl-thiazol-2-yl) hydrazones as MAO-A and MAO-B inhibitors.

Table 5: Structure as well as MAO-A and MAO-B inhibitory activity of [4-(3-methoxyphenyl)-thiazol-2-yl] hydrazine 41-50.

![Structure of [4-(3-methoxyphenyl)-thiazol-2-yl] hydrazine](image)

| CA | X | IC₅₀ (µM) | Selectivity ratio hMAO-A/hMAO-B |
|----|---|-----------|---------------------------------|
| 41 |  | 4.43±0.22 | 5.07±0.13                       | 0.87 |
| 42 |  | 591.80±23.13 | 1.06±0.07                       | 0.56 |
| 43 |  | 836.21±36.58 | 26.64±0.81                       | 31 |
| 44 |  | 1.45±0.04 | 231.02±9.61                       | 6.3 |
| 45 |  | 342.88±15.62 | 6.78±0.25                       | 0.051 |
| 46 |  | 333.05±16.08 | 1.68±0.06                       | 0.2 |
| 47 |  | 457.73±20.35 | 493.83±16.32                       | 0.93 |
| 48 |  | 537.66±27.35 | 2.91±0.13                       | 0.18 |
| 49 |  | 3.64±0.06 | *** <0.036⁶                       |
| 50 |  | *** | **                        |

⁵Inactive at 100 µM (highest concentration tested).
⁶One hundred micromolars inhibits the corresponding hMAO activity by approximately 40-50 %. At higher concentration the compound precipitate.
⁷Values obtained under the assumption that the corresponding IC₅₀ against hMAO-B is the highest concentration tested (100 µM).
Table 6: Structure as well as MAO-B inhibitory activity of 2-(4-(4-halophenyl)thiazol-2-yl) hydrazine 51-56.

| CA  | R           | hIC₅₀ (µM) | hMAO-A | hMAO-B |
|-----|-------------|------------|--------|--------|
| 51  | CH₃         | ***        | 0.79 ± 0.04 |
| 52  | Cl          | ***        | 1.32± 0.05 |
| 53  | H₃CO        | ***        | 2.39± 0.10 |
| 54  | H₃CO        | ***        | 9.24 ± 0.36 |
| 55  | CH₃         | ***        | 0.19 ± 0.01 |
| 56  | H₃C         | **         | 44.74±1.68 |

"Inactive at 100 µM (higher concentration tested). At higher concentration the compounds precipitate.

**100 µM inhibits the corresponding MAO activity by approximately 40-45%. At higher concentration the compounds precipitate.

Table 7: Structure as well as MAO inhibitory activity of 4-substituted-2-(2-(1-pyridin-4-yl) ethylidene) hydrazinyl) thiazole 57-65.

| CA  | Pyridine isomer | R  | hIC₅₀ (µM) |
|-----|-----------------|----|------------|
| 57  | 2-Acetylpyridine | CH₃| No inhibition |
| 58  | 2-Acetylpyridine | COOE| No inhibition |
| 59  | 2-Acetylpyridine | Ph | 16.6±2.01 |
| 60  | 3-Acetylpyridine | CH₃| 6.910±0.227 |
| 61  | 3-Acetylpyridine | COOE| 6.571±0.296 |
| 62  | 3-Acetylpyridine | Ph | 21.3±0.88 |
| 63  | 4-Acetylpyridine | CH₃| No inhibition |
| 64  | 4-Acetylpyridine | COOE| 6.63±0.667 |
| 65  | 4-Acetylpyridine | Ph | 2.67±0.082 |

*p <0.01 or **p<0.05 versus the corresponding IC₅₀ values against hMAO-B, as determined by ANOVA/Dunnett’s.

Conclusion

Based on our interest on heterocyclic chemistry and asymmetric synthesis [24-26], it was concluded that the hybrid scaffold of this series of thiazolyl-hydrazone derivatives could be promising for the discovery of new lead compounds as adjuvants for the treatment of neurodegenerative diseases. A variety of thiazolyl-hydrazone derivatives were prepared, and their MAO inhibitory activity may be used in the treatment of various CNS diseases such as depression, anxiety or Parkinson. A number of researches explored the SAR of thiazolyl-hydrazone derivatives as well as conformation and orientation requirements for binding site through simulation and QSAR studies. Additionally, recognition of a rational picture towards the substitutions responsible for its potency and toxicity may be a future framework in this area.

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