SM Online
Scientific Resources

SM Analytical and Bioanalytical Techniques

Review Article

Synthesis and Structure Activity Relationship of Thiazolyl Hydrazones as Monoamine Oxidase Inhibitors: An Overview

Yagyesh K, Fatima SN and Kapil K*

School of Pharmaceutical Sciences, Apeejay Stya University, India

Article Information

Received date: Jan 25, 2018
Accepted date: Mar 06, 2018
Published date: Mar 07, 2018

***Corresponding author**

Kapil K, School of Pharmaceutical Sciences, Apeejay Stya University, Sohna-Palwal Road, Sohna, Gurgaon, Haryana-122103, India,
Tel: +91-8872041174;
Email: kapil.py@gmail.com

Abbreviations SAR: Structure-Activity Relationship; MAO: Monoamine Oxidase; AO: Amine Oxidase; FAD: Flavin Dinucleotide; hMAO: Human Monoamine Oxidase: CNS: Central Nervous System; QSAR: Quantitative Structure-Activity Relationship

Abstract

Monoamine Oxidise-B is an enzyme which is present in mitochondrial outer membrane. It catalyzes the oxidative deamination of biogenic and xenobiotic amines and plays an important role in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues. In this review, we focused to report the synthesis and structure to activity relationship of substituted thiazolyl hydrazones which are selectively inhibitors of MAO-B enzyme.

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].

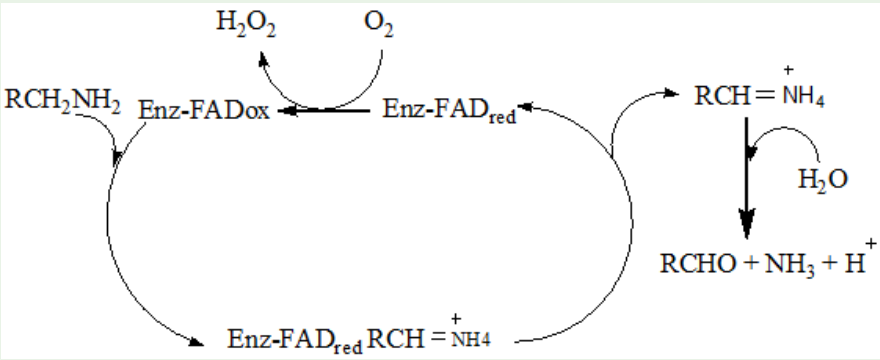


Figure 1: Catalytic pathway for free radical formation by MAO enzyme.

How to cite this article 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.

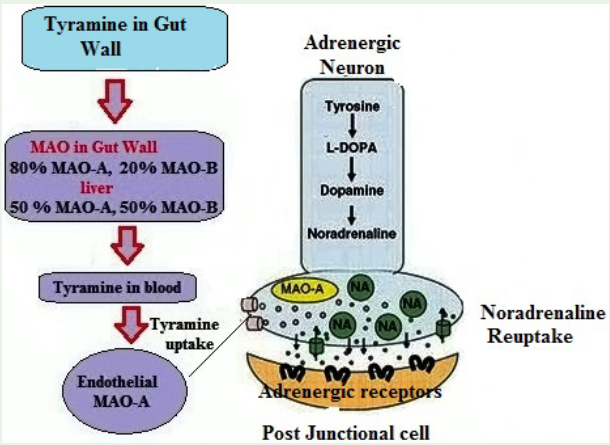
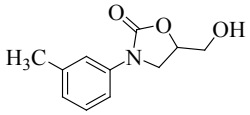
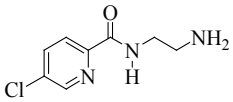
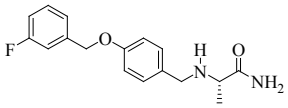
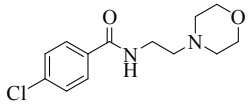
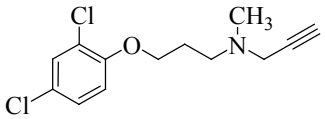
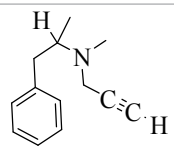
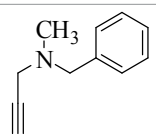


Figure 2: Mechanism of tyramine, the NE release and metabolism after MAO -A inhibition.

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		
Propargyline derivatives		
	Clorgyline [17(e)]	MAO-A
	L-Deprenyl (selegiline) [17(f)]	MAO-B
	Pargyline [17(f)]	MAO-B

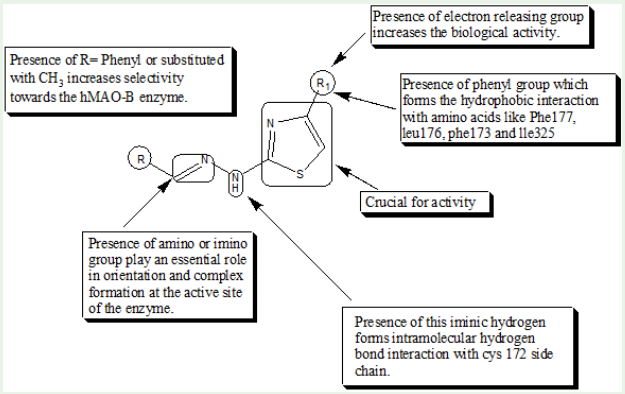


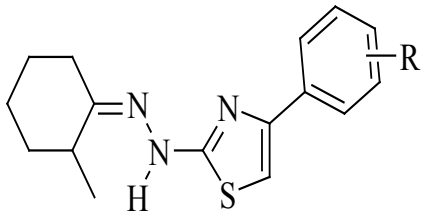
Figure 3: SAR of 2-thiazolyl hydrazone as MAO-A and MAO-B inhibitors.

There are several known reversible and irreversible MAO inhibitors as shown in Table 1 [17, 18].

Structure to activity relationship

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



CA	R	IC_{50}a (μM)		Selectivity Ratio
		hMAO-A	hMAO-B	
1	H	41.23±3.96[b]	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[b]	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[b]	0.014±0.000	1.7
6	$4\text{-}CH_3$	[c]	0.014±0.009	>701[d]
7	$4\text{-}OCH_3$	2.76±0.17[b]	2.37±0.14	1.2
8	$4\text{-}NO_2$	[c]	0.032±0.002	>3693
9	4-CN	31.03±2.44	0.026±0.001	1183

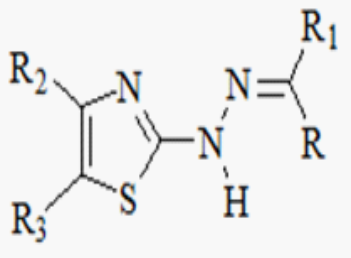
[a]Each IC_{50} value is the mean ± SEM from five experiments (n=5).

[b]level of statistical significance: $P < 0.01$ versus the corresponding IC_{50} values obtained against hMAO-B, as determined by ANOVA/Dunnett's test.

[c]Values obtained under the assumption that the corresponding the compounds IC_{50} against hMAO-A is the highest concentration tested (100 μM).

[d]inactive at 100 μM (highest concentration tested), at higher concentration the compounds precipitate.

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



CA	R	R_1	R_2	R_3	IC_{50} (μM)		
					hMAO-A[b]	hMAO-B(μM)	Ratio
10	CH_3	CH_3	Phenyl	CH_3	2.55±0.17[b]	5.28±0.36	2.08
11	CH_3	CH_2CH_3	Phenyl	CH_3	1.55±0.07[c]	1.53±0.21	1
12	CH_3	$(CH_2)_2CH_3$	Phenyl	CH_3	2.52±0.13[c]	2.31±0.08	0.9
13	CH_3	CH_2CH_3	Phenyl	CH_3	1.65 ± 0.09	2.45 ± 0.14	1.49
14	CH_3	$CH_2CH(CH_3)_2$	Phenyl	CH_3	2.4 ± 0.13[c]	2.78 ± 0.12	1.16
15	CH_3	$CH_2CH_3CH{=}CH_2$	Phenyl	CH_3	6.97±0.43[c]	8.85±0.45	1.27
16	CH_3	$(CH_2)_4CH_3$	Phenyl	CH_3	3.69±0.11[b]	6±0.21	1.64
17	CH_3	$(CH_2)_3CH_3$	Phenyl	CH_3	4.13±0.22	4.78±0.17	1.16
18	CH_2CH_3	$(CH_2)_5CH_3$	Phenyl	CH_3	3.91±0.19[b]	3.75±0.12	1.04
19	CH_3	CH_3	Napthalen-2-yl	H	1.56±0.07[b]	3.55±0.29	2.27
20	CH_3	CH_2CH_3	Napthalen-2-yl	H	1.74±0.08[c]	2.65±0.19	1.52
21	CH_3	$(CH_2)_2CH_3$	Napthalen-2-yl	H	1.81±0.07[c]	3.11±0.16	1.72
22	CH_2CH_3	CH_2CH_3	Napthalen-2-yl	H	1.86±0.06	2.32±0.03	1.25
23	CH_3	$CH_2CH_3(CH_3)$	Napthalen-2-yl	H	2.31±0.16[c]	3.56±0.06	1.54
24	CH_3	$CH_2CH_3(CH_3)$	Napthalen-2-yl	H	1.37±0.08[b]	3.94±0.25	2.86
25	CH_3	$(CH_2)_4CH_3$	Napthalen-2-yl	H	2.45±0.12	15.96±0.45	6.67
26	CH_2CH_3	$(CH_2)_3CH_3$	Napthalen-2-yl	H	2.93±0.12	3.76±0.13	1.28
27	CH_3	$(CH_2)_5CH_3$	Napthalen-2-yl	H	15.48±0.99[b]	D	<6.25[c]

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 antianxiety agents. Preliminary SAR studies revealed that racemic analogues 1-9 (Table 2) are selective as well as biological active for both isoenyzmes 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].

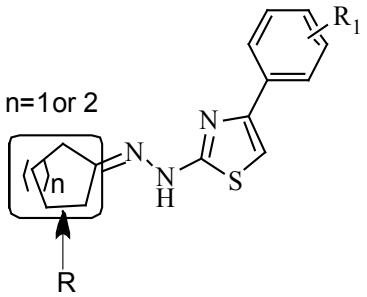
Some of the substituted thiazolyl hydrazones were synthesised and evaluated for MAO Inhibitory activity (Figure 4). In this series substitution was done on C_4 position of the thiazole ring by various electron withdrawing and releasing groups [22] (Table 4).

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 4: Structure as well as MAO-A and MAO-B inhibitory activity of (4-aryl-thiazol-2-yl) hydrazones 28-40.



CA	R	R_1	IC_{50} (μM)		Selectivity ratio
			hMAO-B	hMAO-B	
28	Cyclopentyl	H	7883±91*	296±7	27
29	Cyclopentyl	4-Cl	7160±640*	262±8	27
30	Cyclopentyl	4-F	4443±212*	40±0.9	111
31	Cyclopentyl	2, 4- Cl	54,507±4123*	284±11	192
32	Cyclopentyl	4-NO_2	344±22*	94±3	4
33	Cyclopentyl	4-CN	644±21*	221±2	3
34	Cyclohexyl	H	48,351±1433*	116±5	417
35	Cyclohexyl	4-Cl	2911±171*	211±7	14
36	Cyclohexyl	4-F	1752±21*	4±0.2	438
37	Cyclohexyl	2, 4- Cl	N.E	202±16	495
38	Cyclohexyl	2, 4-F	45754±143*	652±22	70
39	Cyclohexyl	4-CH_3	23371±324*	3689±353	6
40	Cyclohexyl	4-OCH_3	7509±213**	11956±131	0.6

*p<0.01 or **p<0.01 versus the corresponding IC_{50} values obtained against hMAO-B, as determined by ANOVA/Dunnett's. N.E=inactive at 100 μM (highest concentration tested). [b]Value obtained under the assumption that the corresponding IC_{50} against hMAO-A is the highest concentration tested (100 μM).

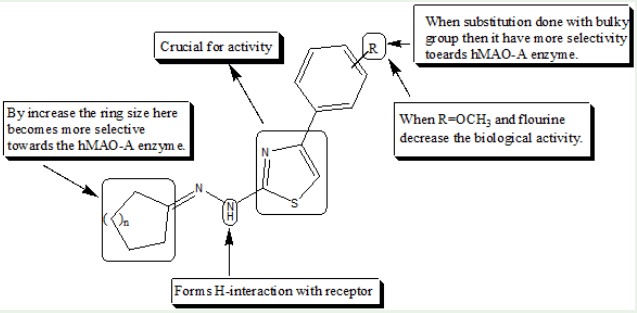
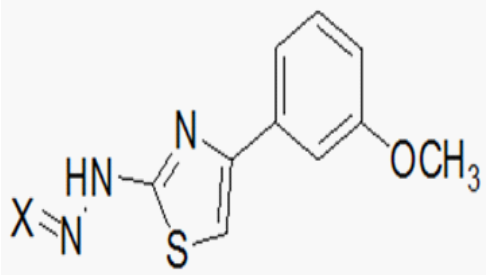
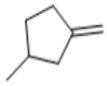
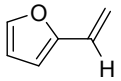
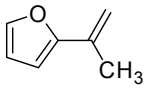
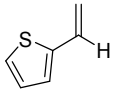
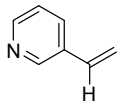
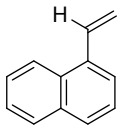
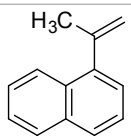


Figure 4: SAR of (4-aryl-thiazol-2-yl) hydrazones as MAO-A and MAO-B inhibitors.

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



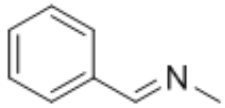
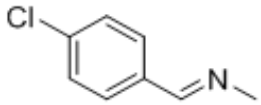
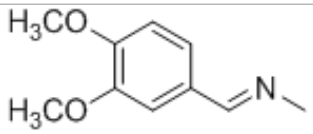
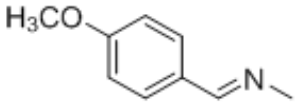
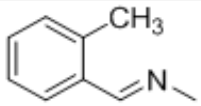
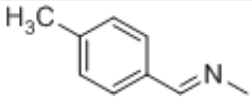
CA	X	IC_{50} (μM)		Selectivity ratio
		hMAO-A	hMAO-B	
41		4.43±0.22	5.07±0.13	0.87
42		591.80±23.13	1.06±0.07	0.56
43		836.21±36.58	26.64±0.81	31
44		1.45±0.04	231.02±9.61	6.3
45		342.88±15.62	6.78±0.25	0.051
46		333.05±16.08	1.68±0.06	0.2
47		457.73±20.35	493.83±16.32	0.93
48		537.66±27.35	2.91±0.13	0.18
49		3.64±0.06	***	<0.036#
50		***	**	

** Inactive at 100 μM (highest concentration tested).

***One hundred micromolars inhibits the corresponding hMAO activity by approximately 40-50 %. At higher concentration the compound precipitate.

Values obtained under the assumption that the corresponding IC_{50} against hMAO-B is the highest concentration tested (100 μM).

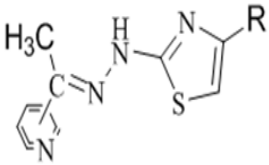
Table 6: Structure as well as MAO-B inhibitory activity of 2-(4-(4-halophenyl thiazol-2-yl hydrazine 51-56.

CA	R	IC_{50} (μM)	
		MAO-A	MAO-B
51		***	0.79 ± 0.04
52		***	1.32± 0.05
53		***	2.39 ± 0.10
54		***	9.24 ± 0.36
55		***	0.19 ± 0.01
56		**	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	IC_{50}(μM)	
			hMAO-A	hMAO-B
57	2-Acetylpyridine	CH_3	No inhibition	No inhibition
58	2-Acetylpyridine	COOEt	No inhibition	No inhibition
59	2-Acetylpyridine	Ph	16.6±2.01	3.84±0.133
60	3-Acetylpyridine	CH_3	6.910±0.227	13.633±0.870
61	3-Acetylpyridine	COOEt	6.571±0.296	0.0722±0.0057
62	3-Acetylpyridine	Ph	21.3±0.88	0.944±0.075
63	4-Acetylpyridine	CH_3	No inhibition	No inhibition
64	4-Acetylpyridine	COOEt	6.63±0.667	0.1274±0.0028
65	4-Acetylpyridine	Ph	2.67±0.082	0.013±0.0012

[a]p <0.01 or [b]p<0.05 versus the corresponding IC_{50} 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-hydrazones derivatives could be promising for the discovery of new lead compounds as adjuvants for the treatment of neurodegenerative diseases. A variety of thiazolyl-hydrazones with MAO inhibitory activity may be used in the treatment of various CNS diseases such as depression, anxiety or Parkinson. A number of researches explored SAR of thiazolyl-hydrazones 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.

References

1. Singh R, Sharma GN. Monoamine Oxidase Inhibitors for neurological disorders: A review. Chem Biol Lett. 2014; 1: 33-39.
2. Griffith GC. Prog Cardiovasc Dis. 1960; 3: 119-133.
3. Greenawalt JW, Schnaitman C. An appraisal of the use of monoamine Oxidase as an enzyme marker for the outer membrane of rat liver mitochondria. J Cell Biol. 1970; 46: 173-179.
4. Harris RS. Thimann KV. Vitamins and hormones. Elsevier. 1944; 2.
5. Gnerre C, Catto MF, Leonetti P, Weber PA, Carrupt, Altomare C, et al. Inhibition of monoamine oxidases by functionalized coumarin derivatives: Biological activities, QSARs and 3D-QSARs. J Med Chem. 2000; 43: 4747-4758.
6. Catto M, Nicolotti O, Leonetti F, Carotti A, Favia AD. Soto-Otero R, et al. Structural Insights into Monoamine Oxidase Inhibitory Potency and Selectivity of 7-Substituted Coumarins from Ligand- and Target-Based Approaches. J Med Chem. 2006; 49: 4912-4925.
7. Youdim MB, Edmondson D, Tipton KF. The therapeutic potential of monoamine Oxidase inhibitors. Nat Rev Neurosci. 2006; 7: 295-309.
8. Gaspar A, Silva T, Yáñez M, Vina D, Orallo F, Ortuso F, et al. Chromone, a Privileged Scaffold for the Development of Monoamine Oxidase Inhibitors. J Med Chem. 2011; 54: 5165-5173.
9. Houslay MD, Tipton KF. The reaction pathway of membrane bound rat liver mitochondrial monoamine oxidase. Biochem J. 1973; 135: 735-750.
10. Bach A, Lan NC, Johnson DL, Abell CW, Bembenek ME, Kwan SW, et al. cDNA cloning of human liver monoamine Oxidase A and B: Molecular basis of differences in enzymatic properties. Proc Natl Acad Sci. 1988; 85: 4934-4938.
11. Erdem SS, Buyukmenekse B. Computational investigation on the structure-activity relationship of the biradical mechanism for monoamine oxidase. J Neur Trans. 2011; 118: 1021-1029.
12. Kearney EB, Salach JI, Walker WH, Seng RL, Kenney W, Zeszotek E, et al. The covalently-bound flavin of hepatic monoamine oxidase.1. Isolation and sequence of a flavin peptide and evidence for binding at the 8alpha position. Eur J Biochem. 1971; 24: 321-327.
13. Yu PH. Studies on the pargyline binding site of different types of monoamine oxidase. Can J Biochem. 1981; 59: 30-37.
14. Stahl SM, Felker A. Monoamine Oxidase inhibitors: A modern guide to an unrequited class of antidepressants. CNS Spectr. 2008; 13: 855-870.
15. Horwitz D, Lovenberg W, Engelman K, Sjoerdsma A. Monoamine Oxidase Inhibitors, Tyramine, and Cheese. JAMA, J Am Med Assoc. 1964; 188: 1108-1110.
16. Davies EB. Tranylcypromine and cheese. Lancet. 1963; 282: 691-692.

17. Yogev-Falach M, Amit T, Bar-Am O, Youdim MB, Amer JF. Soc Exper Biol. 2003; 17: 2325-2327.

17a. Moureau F, Wouters J, Vercauteren DP, Collin S, Evrard G, Durant F, et al. A reversible monoamine Oxidase inhibitor, Toloxatone: Structural and electronic properties. Eur J Med Chem. 1992; 27: 939-948.

17b. Mason RP, Olmstead EG, Jacob RF. Antioxidant activity of the Monoamine Oxidase B inhibitor Lazabemide. Biochem Pharmacol. 2000; 60: 709-716.

17c. Cruz MP, Xadago (Safinamide): A Monoamine Oxidase B Inhibitor for the Adjunct Treatment of Motor Symptoms in Parkinson's disease. P.T. 2017; 42: 622-637.

17d. Korn A, Eichler HG, Fischbach R, Gasic S. Moclobemide, a new reversible MAO inhibitor- interaction with tyramine and tricyclic antidepressants in healthy volunteers and depressive patients. Psychopharmacol. 1986; 88: 153-157.

17e. Gleiter CH, Muhlbauer B, Schulz RM, Nilsson E, Antonin KH, Bieck PR. Monoamine oxidase inhibition by the MAO-A inhibitors brofaromine and Clorgyline in healthy volunteers. J Neural Transm Gen Sect. 1994; 95: 241-245.

17f. Finberg PM, Rabey JM. Inhibitors of MAO-A and MAO-B in Psychiatry and Neurology. Front Pharmacol. 2016; 7: 340.

18. Pletscher A. Significance of MAO inhibition for the pharmacological and clinical effects of hydrazine derivatives. Ann N Y Acad Sci. 1959; 80: 1039-1045.

19. Chimenti F, Carradori S, Secci D, Bolasco A, Chimenti P, et al. J Heterocycl Chem. 2009; 46: 575-578.

20. Hubálek F, Binda C, Khalil A, Li A, Mattevi M, Castagnoli N, et al. Demonstration of isoleucine 199 as a structural determinant for the selective inhibition of human monoamine Oxidase B by specific reversible inhibitors. J Biol Chem. 2005; 280: 15761-15766.

21. Chimenti F, Secci D, Bolasco A. Synthesis and selective inhibition of human monoamine oxidases of a large scaffold of (4, 5-substituted-thiazol-2-yl) hydrazones. Med Chem Comm. 2010; 1: 61-72.

22. Distinto S, Yáñez M, Alcaro S, Cardia MC, Gaspari M, Sanna ML, et al. Synthesis and biological assessment of novel 2-thiazolylhydrazones and computational analysis of their recognition by monoamine oxidase B. Eur J Med Chem. 2012; 48: 284-295.

23. Ramsay RR. Inhibitor design for monoamine oxidases. Curr Pharm Des. 2013; 19: 2529-2539.

24a. Chouhan M, Kumar K, Sharma R, Grover V, Nair VA. NiCl2•6H2O/NaBH4 in methanol: A mild and efficient strategy for chemoselective deallylation/ debenzylation of aryl ethers. Tetrahedron Lett. 2013; 54 4540-4543.

24b. Goyal S, Patel JK, Gangar M, Kumar K, Nair VA. Zirconocene dichloride catalysed one-pot synthesis of pyrroles through nitroalkene-enamine assembly. RSC Adv. 2015; 5 3187-3195.

24c. Kumar V, Kumar K, Pal A, Khatik GL, Nair VA. Aldol reactions of 2-thioxotetrahydropyrimidin-4 (1H)-ones: Stereoregulations from endo-and exocyclic chiral centres. Tetrahedron. 2013; 69: 1747-1754.

24d. Kumar K, Mudshinge SR, Goyal S, Gangar M, Nair VA. A catalyst free, one potential approach for the synthesis of quinoxaline derivatives via oxidative cyclisation of 1, 2-diamines and phenacyl bromides. Tetrahedron Lett. 2015; 56: 1266-1271.

24e. Chouhan M, Senwar KR, Kumar K, Sharma R, Nair VA. Catalytic C-H activation of aryl acetylenes: A fast assembly of 3-(arylethynyl)-3-hydroxyindolin-2-ones using CuI/DBU. Synthesis. 2014; 46:195-202.

24f. Sharma R, Kumar K, Chouhan M, Grover V, Nair VA. Lithium hydroxide mediated synthesis of 3, 4-disubstituted pyrroles. RSC Adv. 2013; 3: 14521-14527.

25a. Goyal S, Patel BK, Sharma R, Chouhan M, Kumar K, Gangar M, Nair VA. Tetrahedron Lett. 2015; 56: 5409-5412.

25b. Kumar K, More SS, Goyal S, Gangar M. Khatik GL, Rawal RK, Nair VA. A convenient synthesis of 4-alkyl-3-benzoylpyrroles from α, β-unsaturated ketones and tosylmethyl isocyanide. Tetrahedron Lett. 2016; 57: 2315-2319.

25c. Kumar K, Siddique J, Gangar M, Goyal S, Rawal RK, Nair VA. ZrCl4 Catalysed Diastereoselective Synthesis of Spirocarbocyclic Oxindoles via [4+2] Cycloaddition. Chem Select 2016; 1: 2409-2412.

25d. Kumar K, Konar D, Goyal S, Gangar M, Chouhan M, Rawal RK, et al. AlCl3/Cyclohexane Mediated Electrophilic Activation of Isothiocyanates: An Efficient Synthesis of Thioamides. Chem Select. 2016; 1: 3228-3231.

25e. Kumar K, Konar D, Goyal S, Gangar M, Couhan M, Rawal RK, et al. Water promoted regiospecific azidolysis and copper catalysed azide alkyne cycloaddition: One-pot synthesis of 3-hydroxy-1-alkyl-3-[(4-aryl/alkyl-1H-1, 2, 3-triazol-1-yl. J Org Chem. 2016; 81 9757-9764.

25f. Kumar K, More SS, Khatik GL, Rawal RK, Nair VA. A Highly Stereoselective Chiral Auxiliary Assisted Reductive Cyclisation of Furoindoline. J Heterocycl Chem. 2017; 54: 2696-2702.

25g. Kaur R, Manjal SK, Rawal RK, Kumar K. Recent synthetic and medicinal perspective of tryptanthrin. Bioorg Med Chem. 2017; 25: 4533-4552.

25h. Manjal SK, Kaur R, Bhatia R, Kumar K, Singh V, Shankar R, et al. Synthetic and medicinal perspective of thiazolidinones: A review. Bioorg Chem. 2017; 75: 406-423.

26a. Mittal M, Kumar K, Anghore D, Rawal RK. ICP-MS: Analytical method for identification and detection of elemental impurities. Curr Drug Discover Tech. 2017; 14: 106-120.

26b. Kaur R, Choudhray S, Kumar K, Gupta MK, Rawal RK. Recent synthetic and medicinal perspectives of dihydropyrimidinones: A review. Eur J Med Chem. 2017; 132: 108-134.

26c. Kumar B, Singh V, Shankar R, Kumar K, Rawal RK. Synthetic and medicinal prospective of structurally modified curcumins. Curr Topics Med Chem. 2017; 17: 148-161.

26d. Talwan P, Choudhary S, Kumar K, Rawal RK. Chemical and medicinal versatility of substituted 1, 4-dihydropyridines. Curr Bioact Compd. 2017; 13: 109-120.

26e. Kaur R, Rani V, Abbot V, Kapoor Y, Konar D, Kumar K. Recent Synthetic and Medicinal Perspectives of Pyrroles: An Overview. J Pharm Chem Chem Sci. 2017; 1: 17-32.