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REVIEW

2nd Heterocyclic Update

Nitrogen heterocycles as potential monoamine oxidase inhibitors: Synthetic aspects

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Abstract The present review highlights the synthetic methods of monoamine oxidase inhibitors (MAO) belonging to a group of nitrogen heterocycles such as pyrazoline, indole, xanthine, oxadiazole, benzimidazole, pyrrole, quinoxaline, thiazole and other related compounds (1990–2012). Moreover, it emphasizes salient findings related to chemical structures and the bioactivities of these heterocycles as MAO inhibitors. The aim of this review is to find out different methods for the synthesis of nitrogen containing heterocycles and their bioactivity related aspects as MAO inhibitors.

Contents

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1. Introduction

Monoamine oxidase (MAO) is an important flavoenzyme present in the outer mitochondrial membrane of neuronal, glial and many other cells and responsible for the oxidative deamination of amines in the brain as well as peripheral tissues, regulating their level (Binda et al., 2007; Youdim and Bakhle, 2006; Novaroli et al., 2006). This reaction produces the corresponding aldehyde and free amine, with the generation of hydrogen peroxide. It exists in two isoforms namely MAO-A and MAO-B that have been identified based on their amino acid sequences, three-dimensional structure, substrate preference, and inhibitor selectivity (De Colibus et al., 2005; Binda et al., 2003; Shih et al., 1999). Dopamine, tyramine, and tryptamine are the substrates for both iso-forms of MAO (Kalgutkar et al., 2001; Ma et al., 2004; Weyler et al., 1990). MAO-A preferentially metabolizes serotonin and noradrenaline and is inhibited by low concentrations of clorgyline (Weyler et al., 1990). MAO-B acts preferentially on 2-phenylethylamine and benzylamine and is inhibited by selegiline (L-deprenyl) (Kalgutkar et al., 2001). Their regulation determines the interest of the monoamine oxidase inhibitors (MAOI) as drugs used in the treatment of neurodegenerative and neurological disorders. In particularly, MAO-A inhibitors are effective in the treatment of depression (Cesura and Pletscher, 1992; Youdim et al., 2004). The MAO-B inhibitors are useful in the management of Parkinson's disease (Guay, 2006; Riederer et al., 2004; Harfenist et al., 1996), their applications were also studied for Alzheimer's disease (Wouters, 1998).

The structural diversity and biological importance of nitrogen containing heterocycles made them striking targets for synthesis and maintained the interest of researchers through many years of historical development of classical organic synthesis (Valverde and Torroba, 2005). Almost many synthetic drugs such as diazepam, benzodiazepines, barbiturates, methotrexate, pesticides, herbicides and some dyes are nitrogen heterocycles. These compounds are of great significance to life because their structural subunits exist in many natural drugs such as papaverine, theobromine, quinine, emetine, etc. (Chin et al., 2006; Koehn and Carter, 2005; Cordell and Farnsworth, 2001; Hughes and Shanks, 2002). Vitamins in B group and the key components of the deoxyribonucleic acid (DNA) molecules are also nitrogen-containing heterocycles (Watson and Crick, 1953; Dahm, 2008).

The classical period of the MAO inhibitors started with hydrazine derivatives. They were originally proposed as tuberculostatic agents, their prototype, iproniazid, was the first modern antidepressant and was introduced into the market under the trade name Marsilid (Cesura and Pletscher, 1992). Subsequently, research has been directed towards the preparation of heterocyclic hydrazines and hydrazides and their potential use as therapeutic agents for the treatment of CNS depression (Tipton, 1972; Mc Kenna et al., 1991; Yamada et al., 1993). Literature survey revealed diversified nitrogen heterocycles, synthesized since decades and tested for their MAO inhibitory potentials. Therefore, the present review emphasizes synthetic aspects of nitrogen heterocycles as MAO inhibitors.

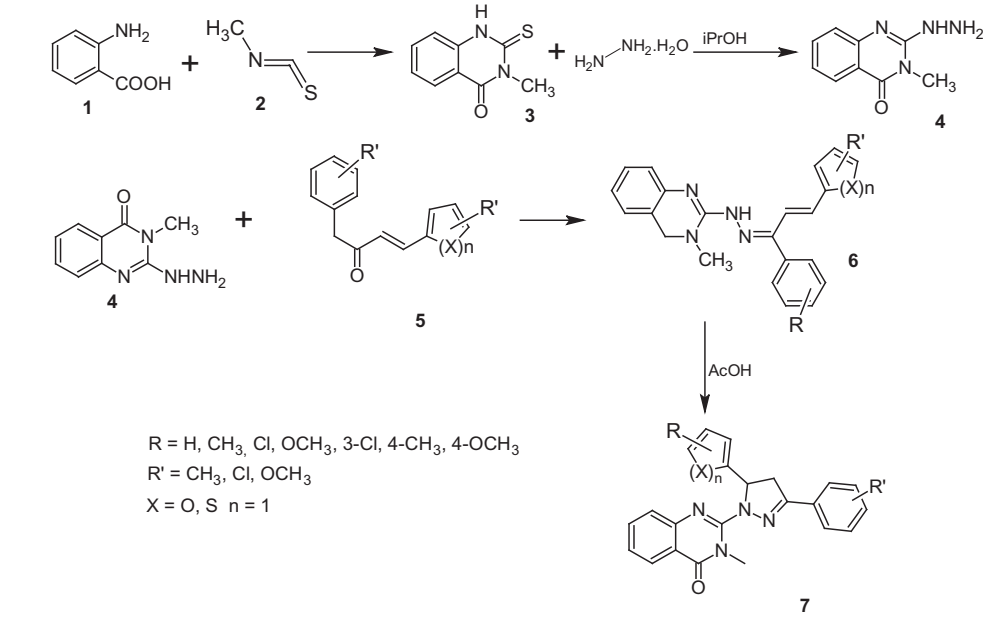
2. Discussion

2.1. Pyrazoline as MAO inhibitor

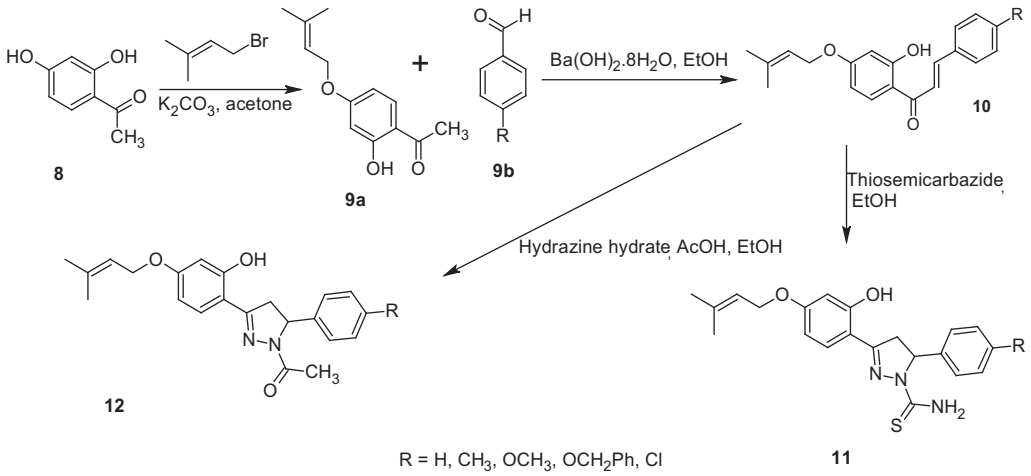
A series of pyrazoline derivatives **7** (Kelekci et al., 2009) have been prepared starting from a quinazolinone ring (Scheme 1). Methyl thioxo quinazolinone was prepared by the reaction of anthranilic acid with methyl isothiocyanate which on further treatment with hydrazine hydrate in 2-propanol (iPrOH) afforded 2-hydrazino-3-methyl-quinazolinone. Substituted chalcones have been synthesized by the Claisen–Schmidt reaction and consequently, they react with **4** and afforded **6,** which were refluxed in glacial acetic acid (AcOH) to result in pyrazoline derivatives. Most of the synthesized compounds showed high activity against MAO-A and MAO-B isoforms.

The synthesis of N-substituted pyrazolines **11** and **12** has been reported (Fioravanti et al., 2010). Synthesis of **10** was achieved by the treatment of 3,3-dimethylallyl bromide with 2,4-dihydroxy-acetophenone. The N-acetyl-3-(2′-hydroxy,4′-prenyloxy)-phenyl-5-phenyl-4,5-dihydro-*(1H)* pyrazole derivatives had been synthesized by the reaction of chalcone with hydrazine hydrate in ethanol (EtOH) while with thiosemicarbazide afforded N-thiocarbamoyl-3-(2′-hydroxy,4′-prenyloxy)-phenyl-5-phenyl-4,5-dihydro-(1*H*) pyrazoles (Scheme 2). Most of the derivatives synthesized, showed an interesting inhibitory activity on MAO-B isoform with no efficacy towards MAO-A.

Synthesis of 3,5-diaryl-1-carbothioamide-pyrazoline derivatives (Scheme 3) has been accomplished with hydroxychalcones (Jayaprakash et al., 2008). Most of the compounds



Scheme 1



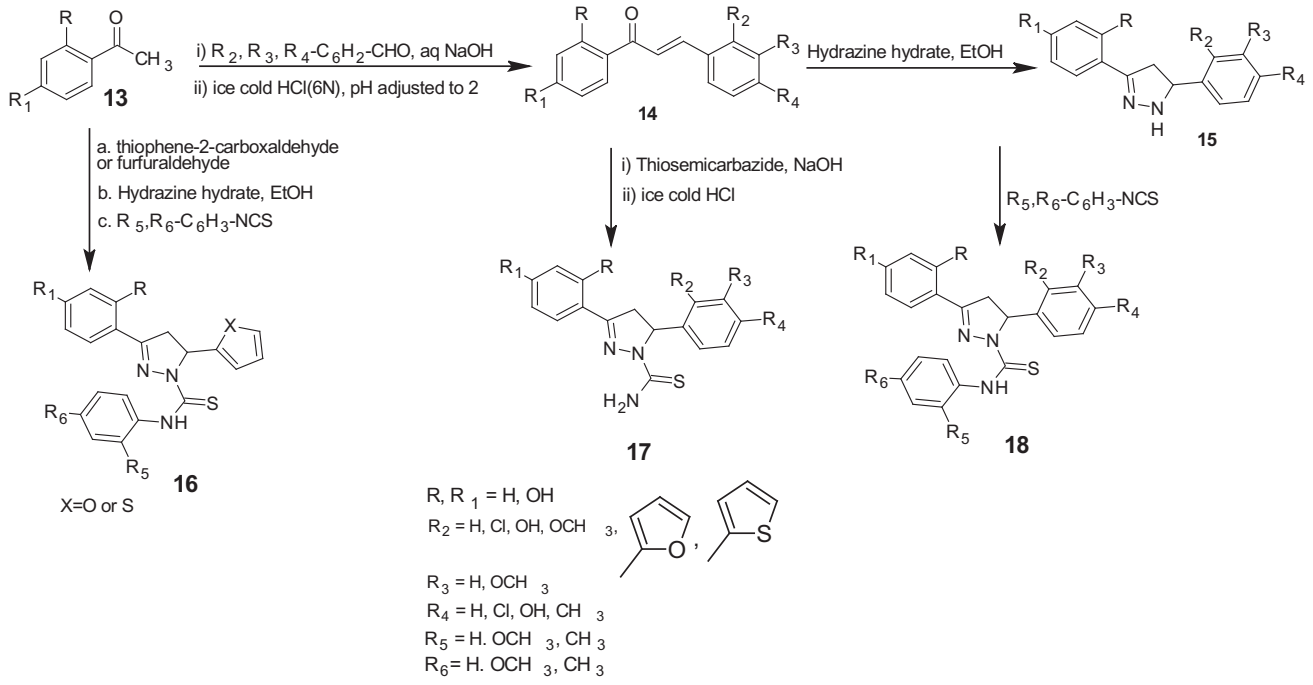
Scheme 2

showed high selectivity against both MAO-A and MAO-B isoforms. Hydroxy chalcones on condensation with hydrazine hydrate (80%) afforded pyrazolines. The final compounds **18** were obtained by the reaction of pyrazoline derivatives with phenyl/substituted phenyl isothiocyanates and compounds **17** were obtained by the reaction of chalcone with thiosemicarbazide in an alkali medium.

Synthesis of pyrazoline derivatives **21** bearing substituted phenyl ring at position 5 carrying unsubstituted ring at 3 positions (Scheme 4a) is reported (Jagrat et al., 2011). Other molecules **23** were prepared without a ring at position 1 carrying an unsubstituted ring at 3 positions (Scheme 4b). Presence of a ring at 1 increases potency as well as selectivity towards MAO-A; however, its absence decreases both potency and selectivity towards MAO-A and MAO-B. The pyrazoline thiocarboxamide derivatives were obtained by the reaction of chalcones with phenyl-isothiocyanates while **23** have been achieved by the condensation of chalcones with hydrazine derivatives (semicarbazide hydrochloride/thiosemicarbazide/amino guanidine bicarbonate).

The cyclization of chalcones **26** with thiosemicarbazides under basic condition (Kelekci et al., 2007) led to the formation of new 1-thiocarbamoyl-3-substituted phenyl-5-(2-pyrrolyl)-4,5-dihydro-*(1H)* derivatives **27** (Scheme 5). Most of the synthesized compounds showed high activity against both MAO-A and MAO-B isoforms.

Few substituted 3-aryl-4,5-dihydropyrazoles-1-carbothioamides have been investigated (Maccioni et al., 2010) from substituted chalcones. All compounds showed a selective activity towards the B isoform of the enzyme, regardless of the substitution on the heterocyclic ring. The key step involves a synthesis of Mannich bases followed by treatment with either

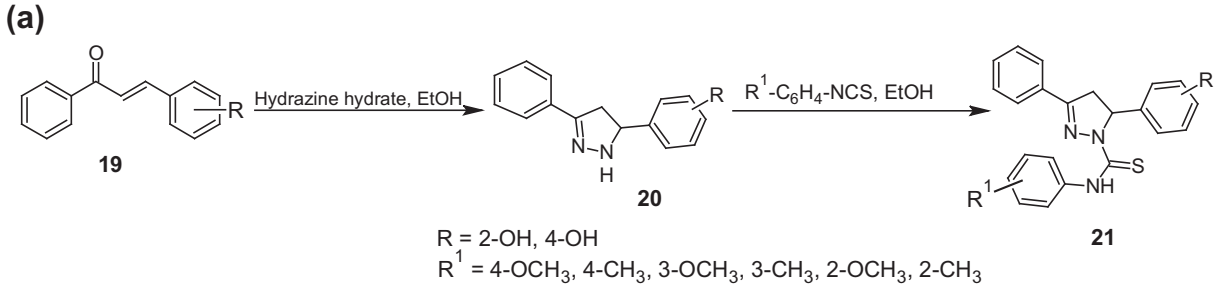


Scheme 3

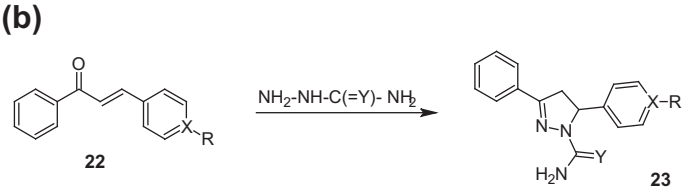
thiosemicarbazide or methyl-thiosemicarbazide generated pyrazoline derivatives **31** (Scheme 6).

The treatment of chalcones with hydrazine hydrate in acetic acid (Manna et al., 2002) resulted in the formation of **35** (Scheme 7). The synthesized compounds proved to be reversible and non-competitive inhibitors of monoamine oxidases, swine kidney oxidase, and bovine serum amine oxidase.

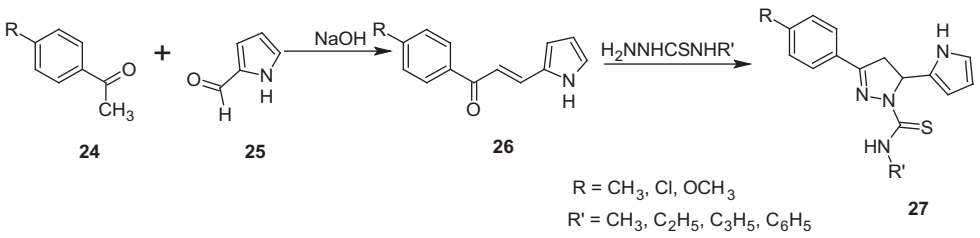
Substituted pyrazoline analogues (Sahoo et al., 2010), have been synthesized (Scheme 8). Few compounds from the series were reversible and selective inhibitors of either MAO-A or MAO-B. Hydroxy chalcones treated with hydrazine hydrate resulted in **37,** further it reacted with benzoyl chloride in pyridine to afford **38**. Reaction of benzene sulphonyl chloride and p-toluene sulphonyl chloride with **37** in tetrahydrofuran



Scheme 4a



Scheme 4b



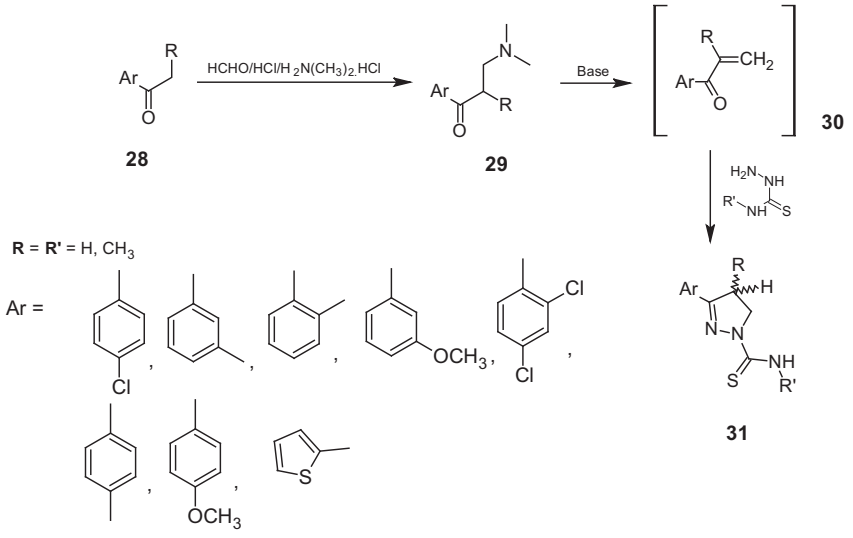
Scheme 5

(THF) yielded **39**. Treatment of chalcone with thiosemicarbazide followed by reaction with methyl iodide and hydroxylamine furnished **41**.

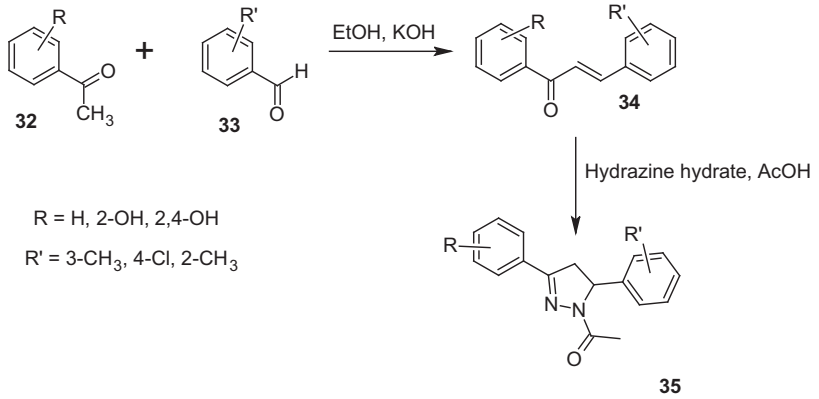
An efficient method (Mishra and Sasmal, 2011) was documented regarding the synthesis of a new series of pyrazoline derivatives **45** bearing an anthracene moiety according to the protocol as shown in (Scheme 9). All the compounds were found selective and reversible towards MAO-B.

The synthesis of N^1-1-propanoyl-3,5,diphenyl-pyrazoline derivatives **49** with MAO-A selectivity, (Scheme 10) has been reported (Chimenti et al., 2008a), which were obtained via the reaction of various chalcones with hydrazine hydrate in propionic acid (PrOH).

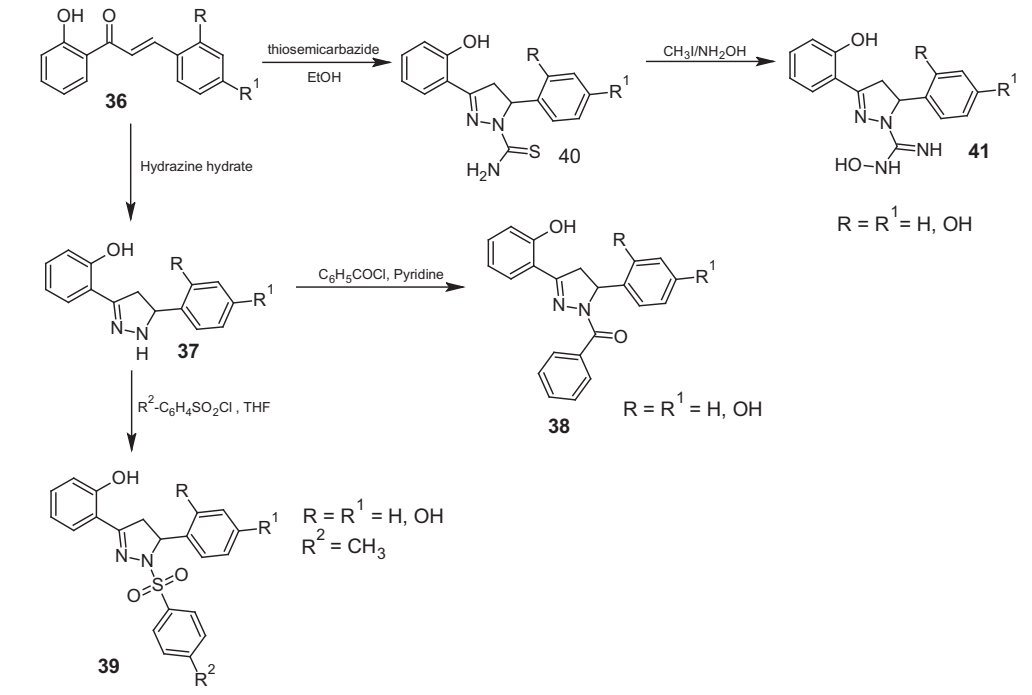
A series of N^1-thiocarbamoyl-3,5-di(hetero)aryl-4,5-dihydro-*(1H)*-pyrazoles were synthesized (Chimenti et al., 2010a) using chalcone as a precursor (Scheme 11). The Claisen–Schmidt condensation of substituted aryl or hetero aryl ketones and aldehydes in the presence of potassium hydroxide gave chalcones. Further, these intermediates were treated with thiosemicarbazide to afford desired derivatives **53.** Some of these compounds were endowed with a selective inhibitory activity against MAO-B.



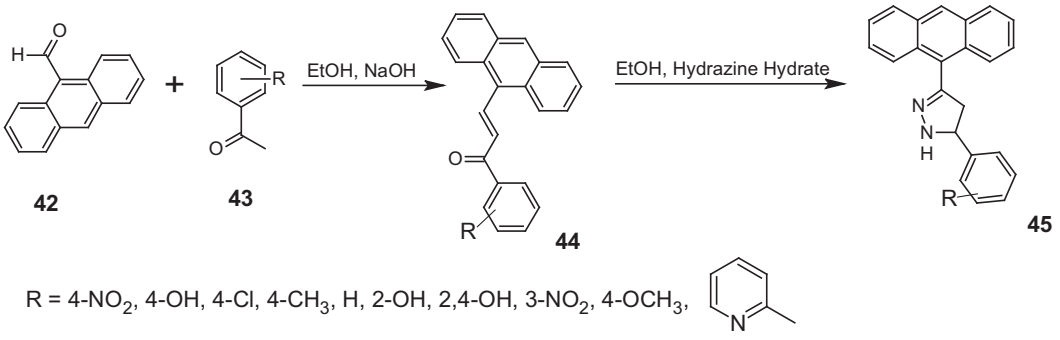
Scheme 6



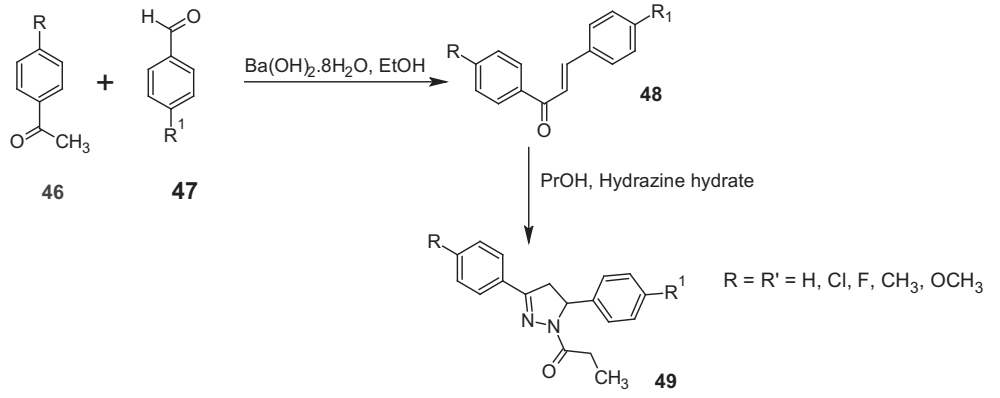
Scheme 7



Scheme 8

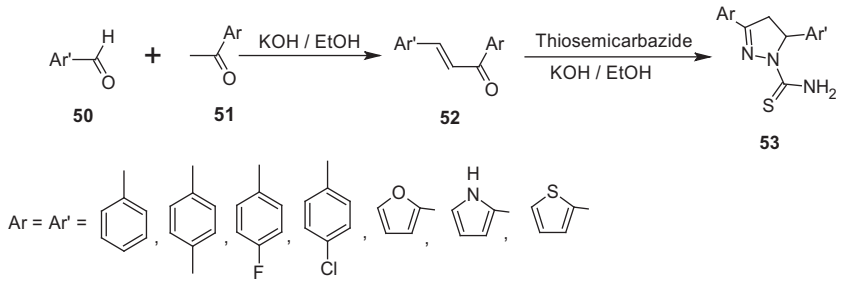


Scheme 9

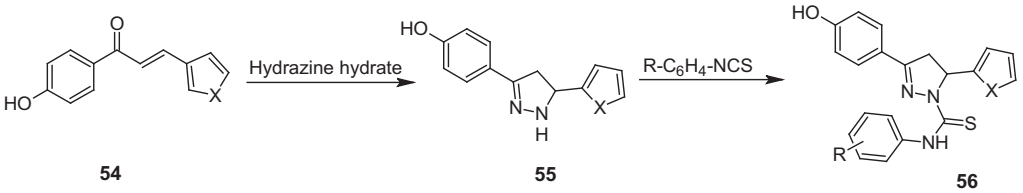


Scheme 10

The functionally substituted pyrazole derivatives **56** have been reported (Karuppasamy et al., 2010). The compounds were found to be reversible and selective MAO-A inhibitors. The 4-hydroxychalcones treated with excess hydrazine hydrate furnished **55,** which further (Scheme 12) reacts with respective phenyl isothiocyanate and resulted in desired compounds.



Scheme 11



Scheme 12

A novel series of 1-acetyl-3-(4-hydroxy and 2,4-dihydroxyphenyl)-5-phenyl-4,5-dihydro-*(1H)* pyrazole derivatives (Chimenti et al., 2004) have been synthesized from chalcones **59** and **64** (Scheme 13). The 4-hydroxy chalcones are obtained via the Claisen–Schmidt reaction. In the synthesis of **64,** the hydroxyl group was protected with 3,4-dihydro-α-pyran before the condensation reaction. The protected acetophenone reacts with the aldehyde to form the protected chalcone, which was subsequently formed by hydrolysis. Chalcones then treated with hydrazine hydrate to afford acetyl pyrazoline derivatives **66.** The new synthesized compounds proved to be more reversible, potent, and selective inhibitors of MAO-A than of MAO-B.

A series of thiocarbamoyl pyrazoline derivatives **70** (Chimenti et al., 2005) were synthesized (Scheme 14). All the synthesized compounds showed high activity against both MAO-A and MAO-B isoforms. Chalcones were treated with thiosemicarbazides to afford the target derivatives.

Synthesis of pyrazoline derivatives (Chimenti et al., 2006) has been accomplished through the reaction of chalcones with hydrazine derivatives (Schemes 15a and 15b). Triphenyl 2-pyrazoline derivatives **74** were synthesized by the action of 4-chlorophenyl hydrazine hydrochloride on chalcone while acetyl 2-pyrazoline **75** was achieved through the reaction of hydrazine hydrate with chalcones (Scheme 15a). Most of the new synthesized compounds proved more reversible, potent, and selective inhibitors of MAO-A than of MAO-B. The synthesis of 1,3-diphenyl-4,5-dihydro-*(1H)*-pyrazole derivatives **78** and 1-acetyl-3-phenyl-4,5-dihydro-*(1H)*-pyrazole derivatives **79** involves the cyclization of an intermediate Mannich base with phenyl hydrazine and hydrazine hydrate respectively (Scheme 15b).

2.2. Indole as MAO inhibitor

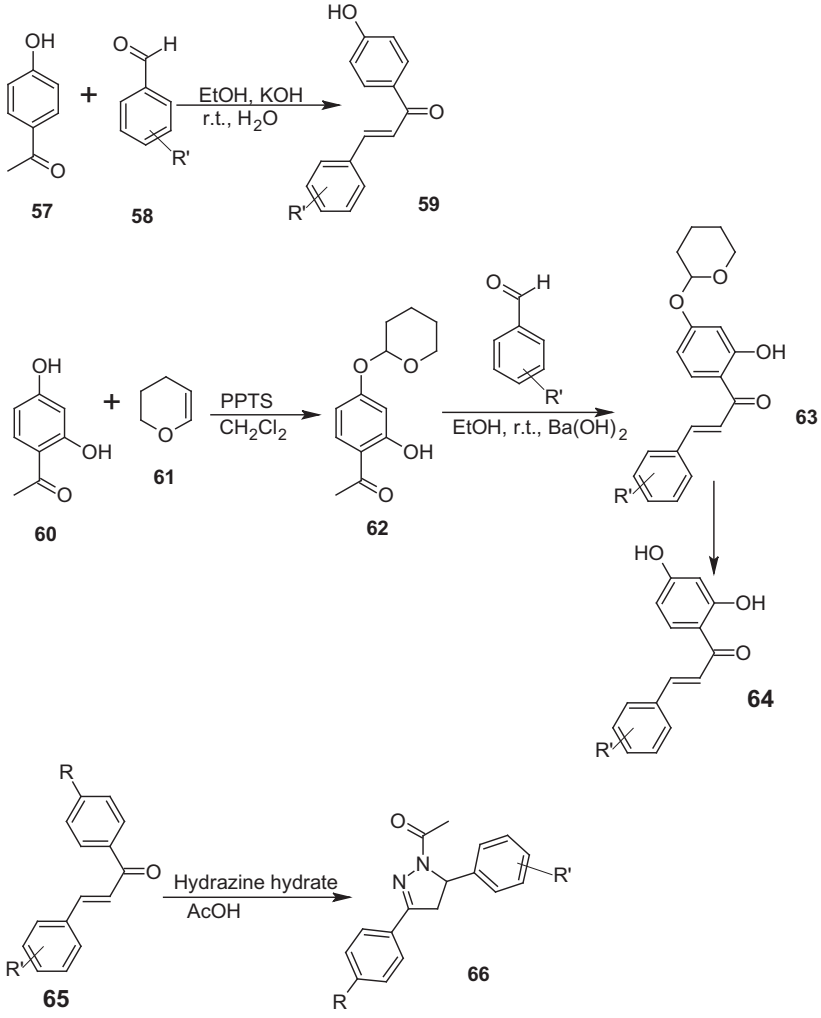
The 3-indolylcoumarin derivatives **82** (Delogu et al., 2011) have been prepared through the Perkin reaction of o-hydroxybenzaldehydes and acetic acids in dimethyl sulphoxide (DMSO), using N,N'-dicyclohexylcarbodiimide (DCC) as dehydrating agent (Scheme 16). The synthesized derivatives were found to be selective MAO-B inhibitors.

The synthesis of 3 substituted indolyl amides **84** by the reaction of indole-2-carboxylic acid with appropriate amines at room temperature in the presence of (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium-hexafluorophosphate (BOP) had been studied (Regina et al., 2008). Several compounds from the series were potent MAO-A as well as MAO-B inhibitors. Few derivatives **85** have been achieved by the alkylation of few derivatives 84b by means of iodomethane through a phase-transfer reaction in the presence of tetrabutylammonium hydrogen sulphate (TBAHS). The reduction of some derivatives from the series with lithium aluminium hydride ($LiAl_4$) in tetrahydrofuran (THF), afforded amine derivatives **86** (Scheme 17).

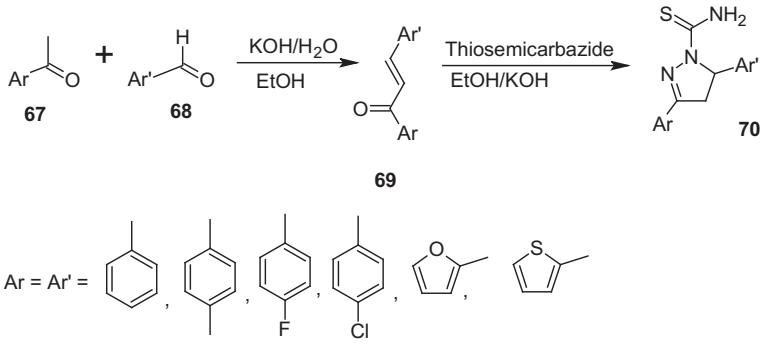
Beta–carboline derivatives **89** were synthesized from harmine (Scheme 18). The two-step procedure involves the demethylation of harmine to the corresponding harmol (Reniers et al., 2011) followed by re-alkylation of harmol to the corresponding carboline derivatives. The O-alkylated compounds with lipophilic groups like cyclohexyl, phenyl and aliphatic chains increased the inhibition of MAO-A compared to harmine.

Several indole derivatives **92** with selectivity towards MAO-B have been synthesized (Prins et al., 2010) by reacting 5-amino-2-methylindole with appropriate carboxylic acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) (EDC) or DCC as a dehydrating agent (Scheme 19).

The methylated branched indole analogues were (Garcia et al., 1992) obtained following the synthetic route (Scheme 20a). Aldehyde was the key intermediate obtained from ethyl 2-indolecarboxylate by the reduction with $LiAl_4$ followed by oxidation with manganese dioxide. Condensation of **94** with sulphamide followed by methyllithium addition and hydrolysis



Scheme 13

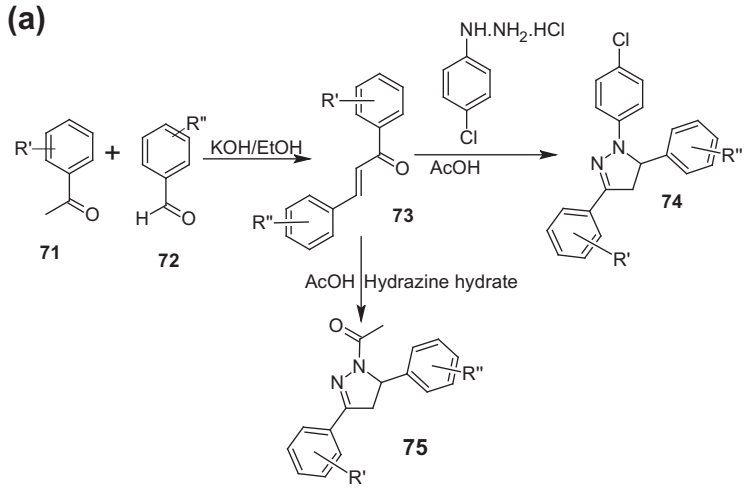


Scheme 14

yielded primary amine **97.** Compounds **98** and **102** were obtained by the reaction of aldehyde with the suitable amines, followed by treatment of the analogues with organometallic reagents. Most of the synthesized analogues were found to be selective with the MAO-B inhibitors. (See Scheme 20b).

The amine was N-alkylated in the presence of t-butylamine by the respective alkyl bromide to give the corresponding amines **100.**

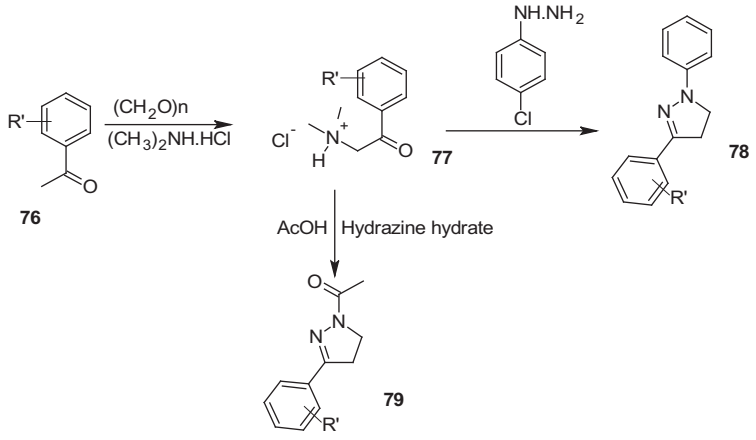
The Cur–Gus reaction of acid with diphenylphosphoryl azide ($N_3PO(OPh)_2$) and triethylamine (Et_3N) gave the carbamate,



R' = H, 2-OH, 2,4-OH, 2,6-OH, 4-OH,2-CH_3, 2-Cl, 2-Br, 2-NO_2,3-CH_3, 4-CH_3, 3-OCH_3, 4-OCH_3,2,4-OCH_3, 2-NO_2, 2,5-OCH_3

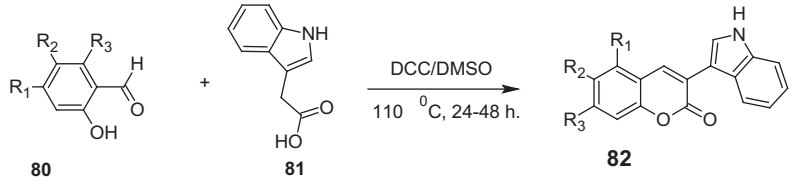
R" = H, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2,4-Cl, 2-CH_3, 4-CH_3, 2-OCH_3, 3-OCH_3, 4-OCH_3, 2,3-OCH_3, 2,5-OCH_3, 3.4-OCH_3, 3-NO_2, 4-NO_2

Scheme 15a



R' = H, 2-OH, 2,4-OH, 2,6-OH, 4-OH,2-CH_3, 2-Cl, 2-Br, 2-NO_2,3-CH_3, 4-CH_3, 3-OCH_3, 4-OCH_3,2,4-OCH_3, 2-NO_2, 2,5-OCH_3

Scheme 15b



R_1, R_2, R_3 = H, OCH_3

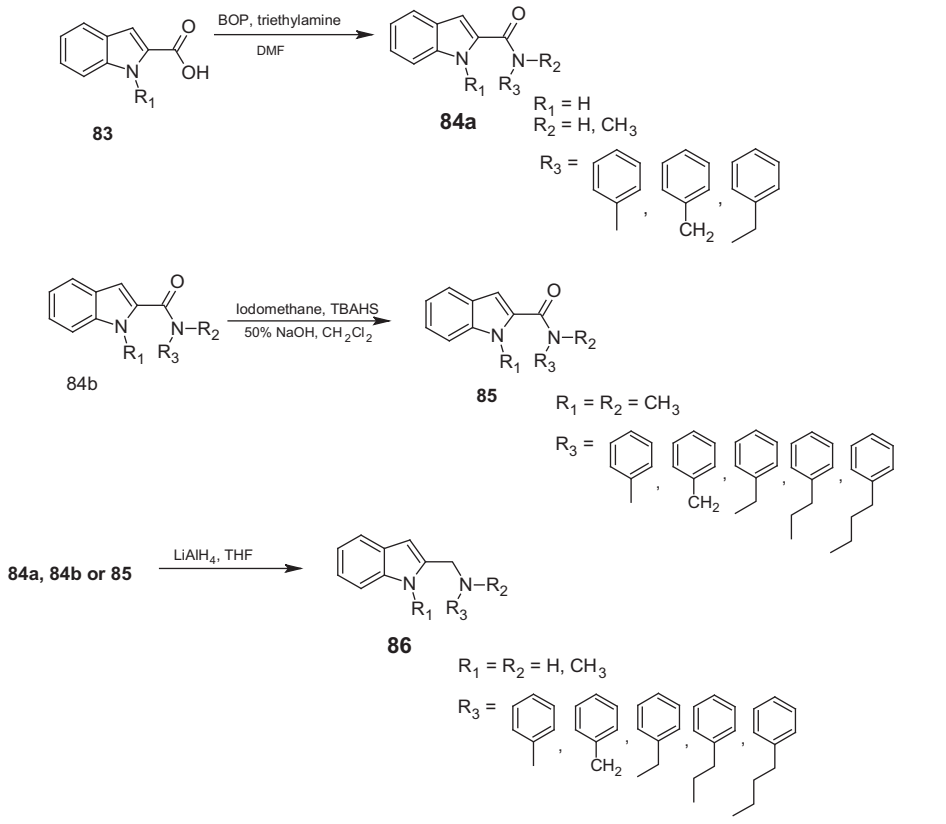
Scheme 16

which under catalytic hydrogenation yielded **106**. On the other hand, N-methylation of **105** with sodium hydride (NaH) and methyl iodide gave **107** which were hydrogenated to **108**.

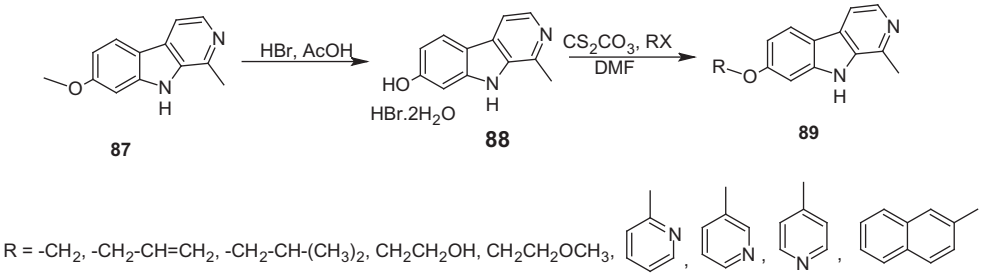
The amines **114** and **115** have been synthesized (Scheme 20c). The Wittig reaction of the aldehyde with (methoxycarbonylmethylene)-triphenyl phosphorane gave **110**. Catalytic hydrogenation followed by treatment with ammonia and methylamine in methanol under potassium cyanide catalysis afforded desired derivatives.

2.3. Xanthine as MAO inhibitor

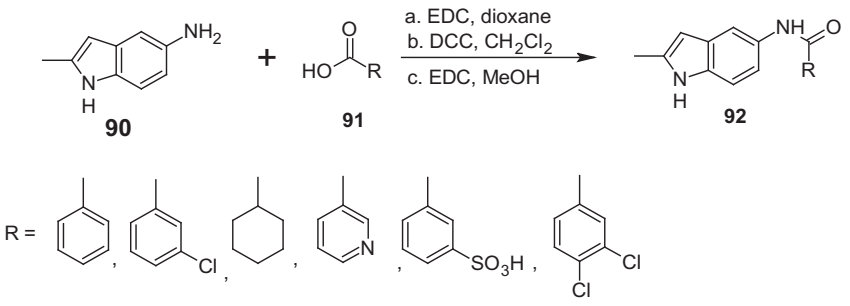
Recently, a series of 8-substituted phenylxanthines (Schemes 21a and 21b) have been prepared (Song et al., 2012).



Scheme 17



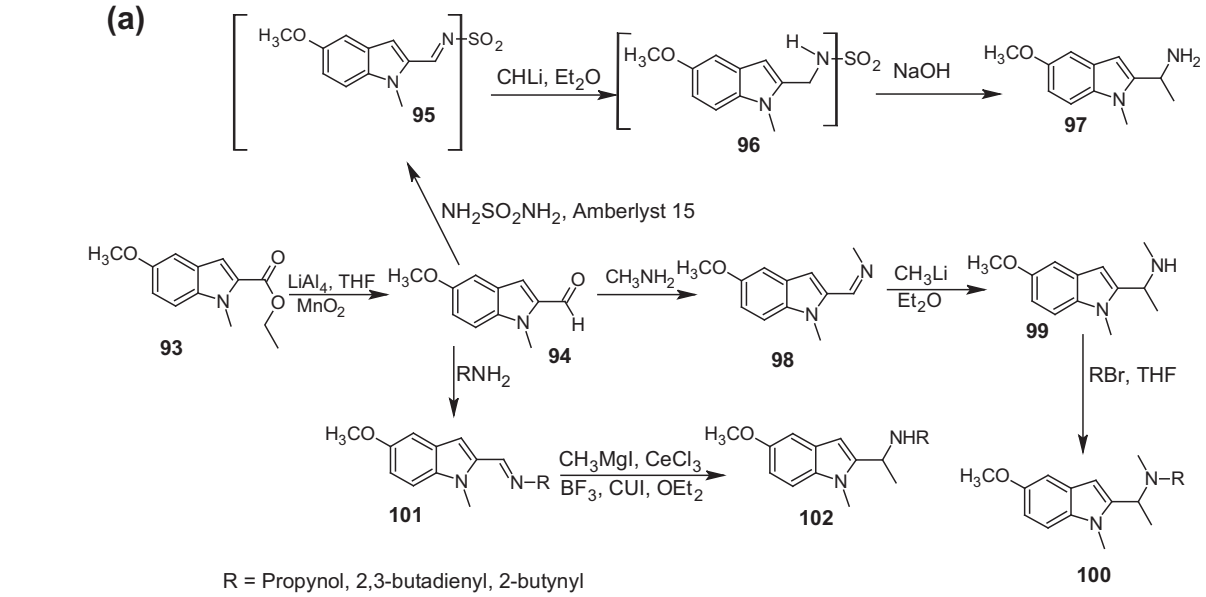
Scheme 18



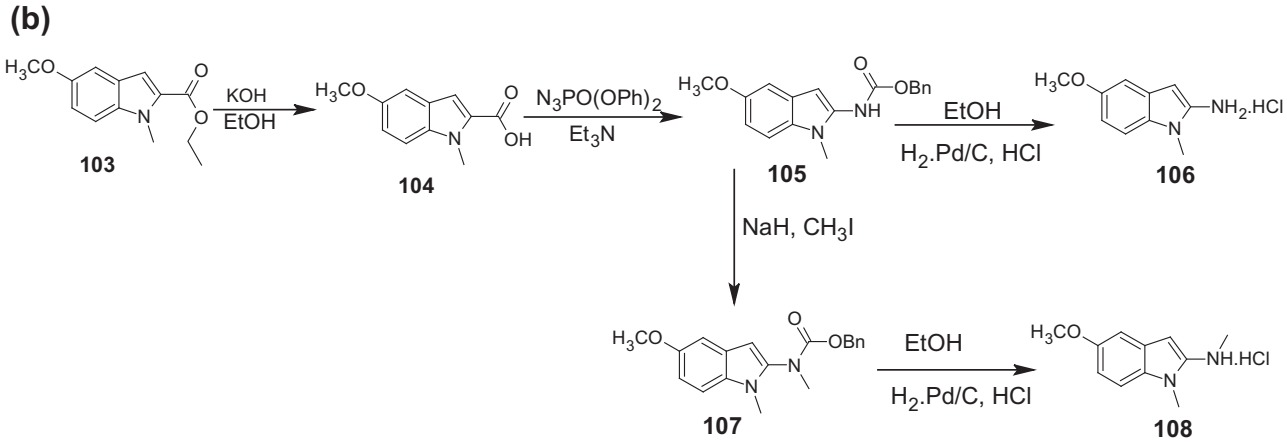
Scheme 19

Substituted benzamido benzoic acids were synthesized by a base catalysed reaction of para or meta substituted aminobenzoic acid in dichloromethane with substituted benzoyl chloride (Scheme 21a).

The key starting compound, 5,6-diamino-1,3-dimethyl uracil **121** had been coupled with **118** followed by cyclization using base EDCl, and furnished substituted 8-(benzamido)-phenylxanthine which on methylation with iodomethane



Scheme 20a



Scheme 20b

afforded 123 (Scheme 21b). All the synthesized compounds were found to be selective MAO-B inhibitors.

An efficient method has been reported regarding the synthesis of (E)-2-strylxanthine analogues (Petzer et al., 2003) according to the protocol (Schemes 22a and 22b). The results of this study demonstrated that the entire (E)-8-styrylxanthinyl analogues had significant MAO-B inhibitory properties. Amides have been accomplished by the acylation of 1, 3-diethyl or 1,3-dimethyl-5,6-diaminouracil with substituted cinnamic acid in the presence of EDAC, which on cyclization afforded corresponding 1,3-disubstituted (E)-8-strylxanthinyl derivatives. Methylation of **126** with iodomethane afforded methyl analogues **127.** Photochemical isomerisation of certain (E)-strylxanthines yielded **128** derivatives (Scheme 2).

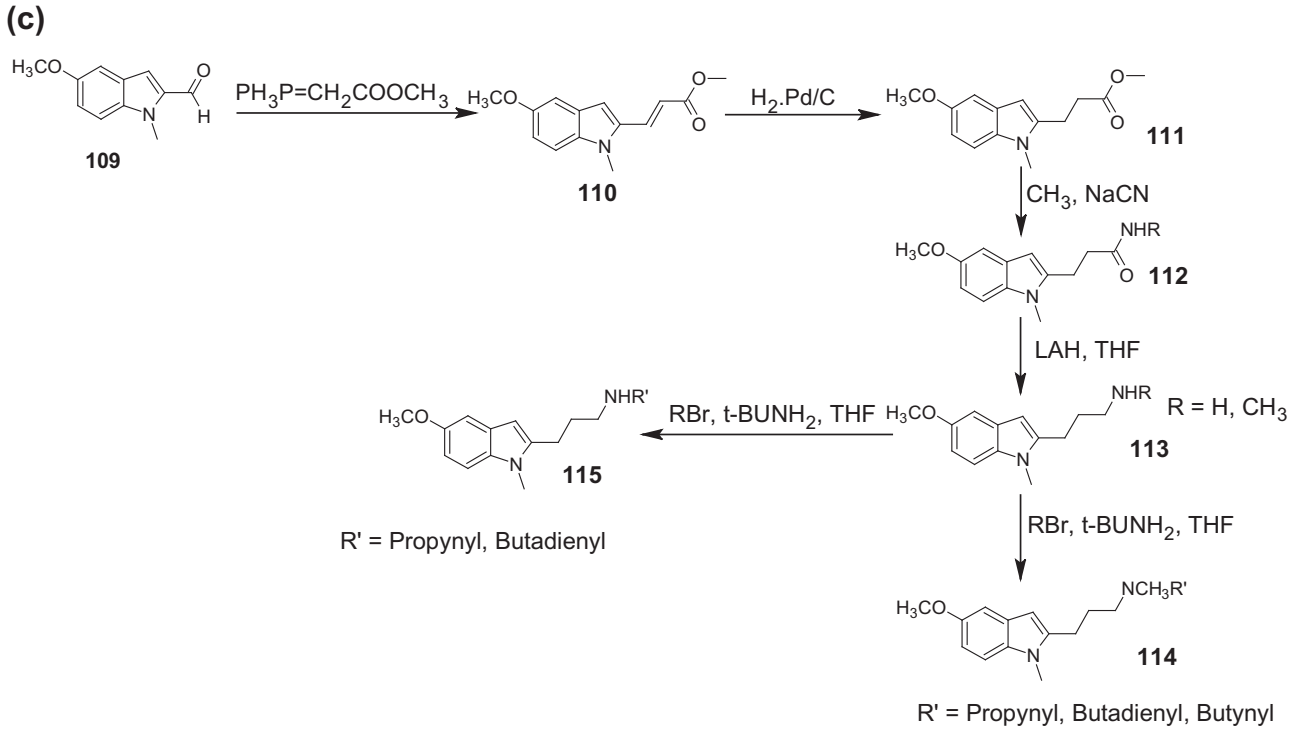
Several (E)-8-strylcaffenyl derivatives **132** (Scheme 23) have been prepared (Berg et al., 2007). The key starting material 1,3-dimethyl-5,6-diaminouracil was reacted with appropriate carboxylic acid in the presence of EDAC activating reagent. The resulting amide underwent a ring closure reaction and furnished 1,3-dimethyl-8-substituted-*7H*-xanthinyl analogues **131.** Methylation of **131** with excess of iodomethane in potassium carbonate resulted in the target derivatives. The results of these studies have shown that all the synthesized analogues exhibited significant MAO-B inhibitory properties.

The two series of 8-(substituted-styrol-formamido)-phenylxanthine derivatives **144** (Suwen et al., 2012) were synthesized (Scheme 24). All the synthesized derivatives exhibited significant MAO-B inhibitory properties.

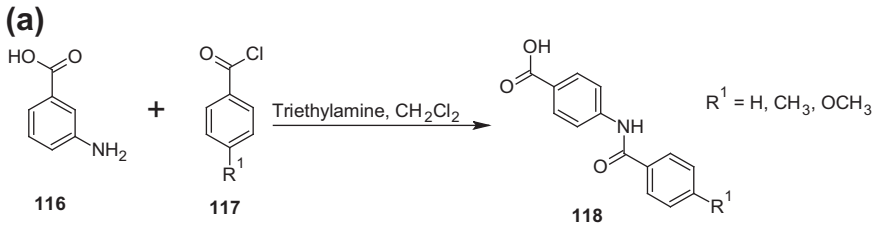
The amidyl intermediate formed underwent ring closure when heated under reflux in aqueous sodium hydroxide to yield corresponding 1,3-dimethyl-8-substituted-*7H*-xanthinyl analogues **141 and 142** and were selectively 7 N methylated with an excess of iodomethane and potassium carbonate to yield 1,3,7-trimethyl-8-substituted xanthinyl derivatives. (See Scheme 25).

2.4. Oxadiazole as MAO inhibitor

An interesting method has been reported (Ke et al., 2009) for the synthesis of a series of *4H*-1,3,4-oxadiazin-5*(6H)*-ones.



Scheme 20c



Scheme 21a

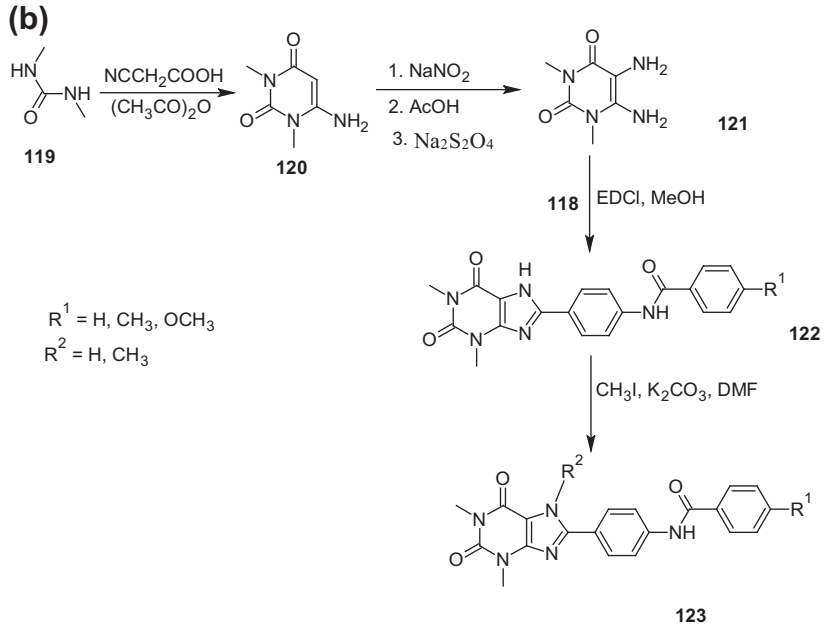
Some of the compounds displayed moderate to good inhibitory activities towards MAO. The condensation of hydrazides and nonan-5-one followed by a selective reduction of nitriles using sodium borohydride ($NaBH_4$) led exclusively to the key N alkylated intermediates, on the other hand N-alkylated products **148** were obtained by the Michel addition of α, β-unsaturated systems such as acrylonitrile and n-butyl acrylate. Cyclization of **147** and **148** using chloroacetyl chloride gave target compounds **149**.

The monosubstituted and disubstituted aroylhydrazines have been obtained by the Michael addition of the acrylonitrile on the corresponding aroylhydrazines. Different 5-aryl-1,3,4-oxadiazol-2(3*H*)-one derivatives (Mazouz et al., 1990) were synthesized by the reaction of phosgene with appropriate monosubstituted hydrazines (Scheme 26a), while **153** was generated by treatment of the corresponding aroylhydrazines with thiophosgene. The most active compounds in the proposed series acted preferentially against MAO-B while other derivatives against MAO-A.

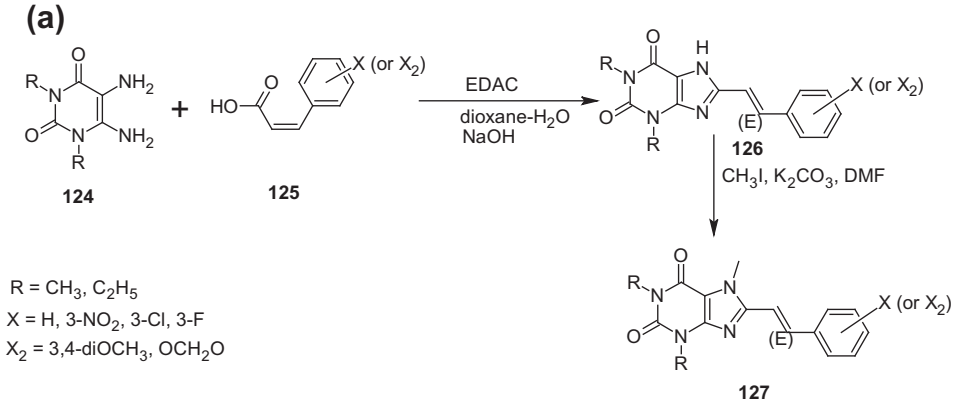
Several thiadiazolone analogues **160** were reported (Scheme 26b). Treatment of 4-biphenylyldithiocarbonyloxy-acetic with (2-cyanoethyl) hydrazine gave 1-(4- biphenylylthiocarbonyl)-2-(2-cyanoethyl)-hydrazine. Subsequent reaction of **159** with phosgene or thiophosgene afforded the corresponding substituted thiadiazolone and thiadiazolethione derivatives.

A series of 1,3,4-oxadiazole-3*(2H)*-carboxamide (Ke et al., 2008) derivatives have been synthesized by direct hetero-cyclization of substituted benzoylisocyanate with a variety of aroylhydrazines (Scheme 27). The preliminary results showed that most of the compounds have moderate inhibitory activities towards MAO. Substituted aroylhydrazones were prepared by three-step reactions viz. esterification using sulphuric acid followed by hydrazination via hydrazine hydrate and finally condensation with nonane-5-one. Substituted benzoylisocyanate reacts with aroylhydrazone afforded **163** while the appropriate aroylhydrazone was refluxed in acetic anhydride (Ac_2O) and yielded **164.**

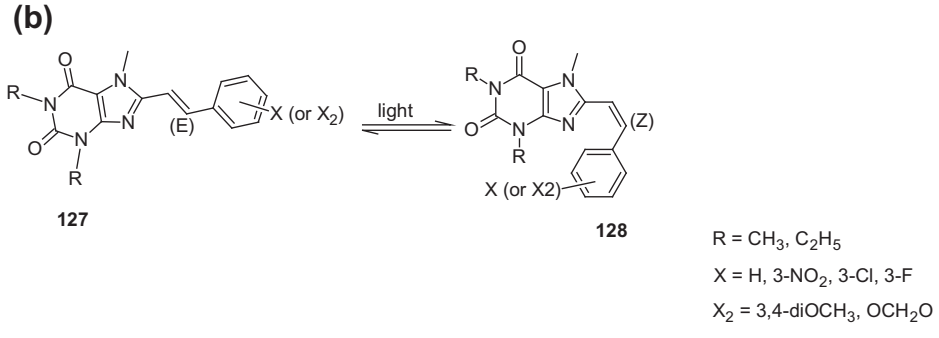
Synthesis of 3-acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazole derivatives **168** (Maccioni et al., 2011) have been accomplished through the reaction of N^1-arylidenearylhydrazides with acetic anhydride (Scheme 28). These 1,3,4-oxadiazoles derivatives were found to be promising reversible and selective MAO-B inhibitors.



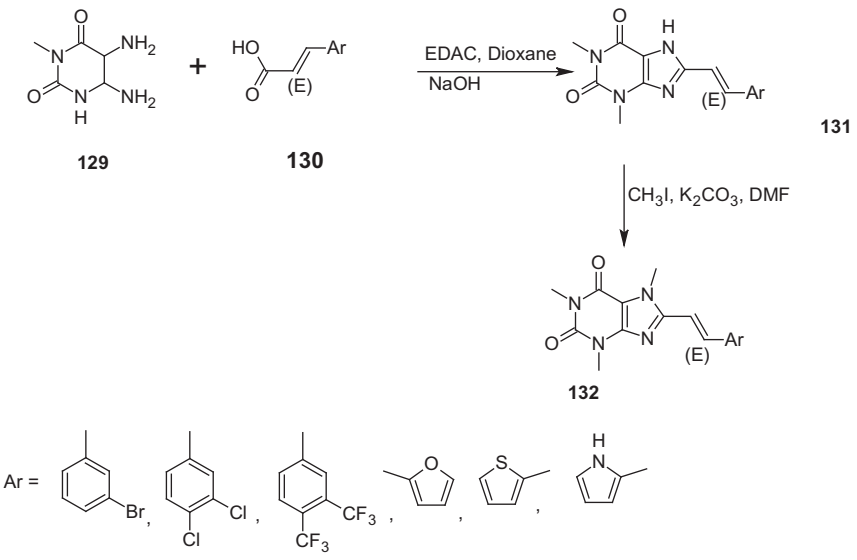
Scheme 21b



Scheme 22a



Scheme 22b



Scheme 23

2.5. Quinoxaline as MAO inhibitor

A facile, microwave assisted synthesis (Hassan et al., 2006) of aminoquinoxalines has been achieved by the reaction of 2-benzyl-3-chloroquinoxaline and the primary amine (Scheme 29). All the synthesized compounds showed more selective inhibitory activity towards MAO-A than MAO-B.

A series of 2-benzyl-3-(2-arylidenehydrazinyl)-quinoxalines substituted 1-aryl-[1,2,4] triazolo [4,3-a]-quinoxaline analogues (Khattab et al., 2010) were synthesized (Scheme 30). Most of the synthesized compounds have been found to be MAO-A selective. Substituted carbonyl compound reacts with **172** and afforded the parallel Schiff bases. Annelation of **173** by pyrolysis in aprotic polar solvent like DMF led to the formation of their corresponding 1-aryl-4-benzyl-[1,2,4]triazolo[4,3-a]quinoxalines. On the other hand, **176** were obtained when Schiff bases exposed to acylation with acetic anhydride in pyridine. Alternatively, using copper (II) chloride in DMF as a promoter for the annelation reaction via double oxidation processes afforded compounds **175** with excellent yields.

2.6. Pyrrole as MAO inhibitor

Synthesis of 1-methyl-3-phenylpyrrole derivatives **179** as selective MAO-B inhibitors was reported (Ogunrombi et al., 2008) and were obtained via the cyclization of **178** using sodium methoxide in anhydrous pyridine (Scheme 31).

A series of N-methyl-2-phenylmaleimidyl analogues (King et al., 2009) have been reported (Scheme 32). All the synthesized derivatives were selective MAO-B inhibitors. Initially, substituted aniline was diazotized and treated with N-methylmaleilide according to the modified Meerwein reaction. Finally, **183** were obtained by the dehydrohalogenation of intermediate chloro succinimide in the presence of 2,6-lutidine.

2.7. Benzimidazole as MAO inhibitor

The (E)-2-strylbenzimidazole derivative **188** (Berg et al., 2007) has been synthesized (Scheme 33). The results of these studies showed that all synthesized compounds exhibited a significant MAO-B inhibitory potency. The condensation of o-phenylenediamine with appropriately substituted cinnamic acid in the presence of EDAC was carried out. Cyclization of intermediate **186** in the presence of hydrochloric acid followed by methylation with methyl iodide afforded strylbenzimidazole.

A series of (E)-2-strylbenzimidazole derivatives **193** (Petzer et al., 2003) were synthesized according to the protocol (Scheme 34). The key intermediate 2-methyl-*1H*-benzimidazole was prepared according to Phillips by the condensation of o-phenylenediamine with acetic acid. Consequently, it was treated with benzaldehydes to afford **192,** which on treatment with iodomethane yielded (E)-1-methyl-2-strylbenzimidazole analogues. All the synthesized derivatives exhibited significant MAO-B inhibitory properties.

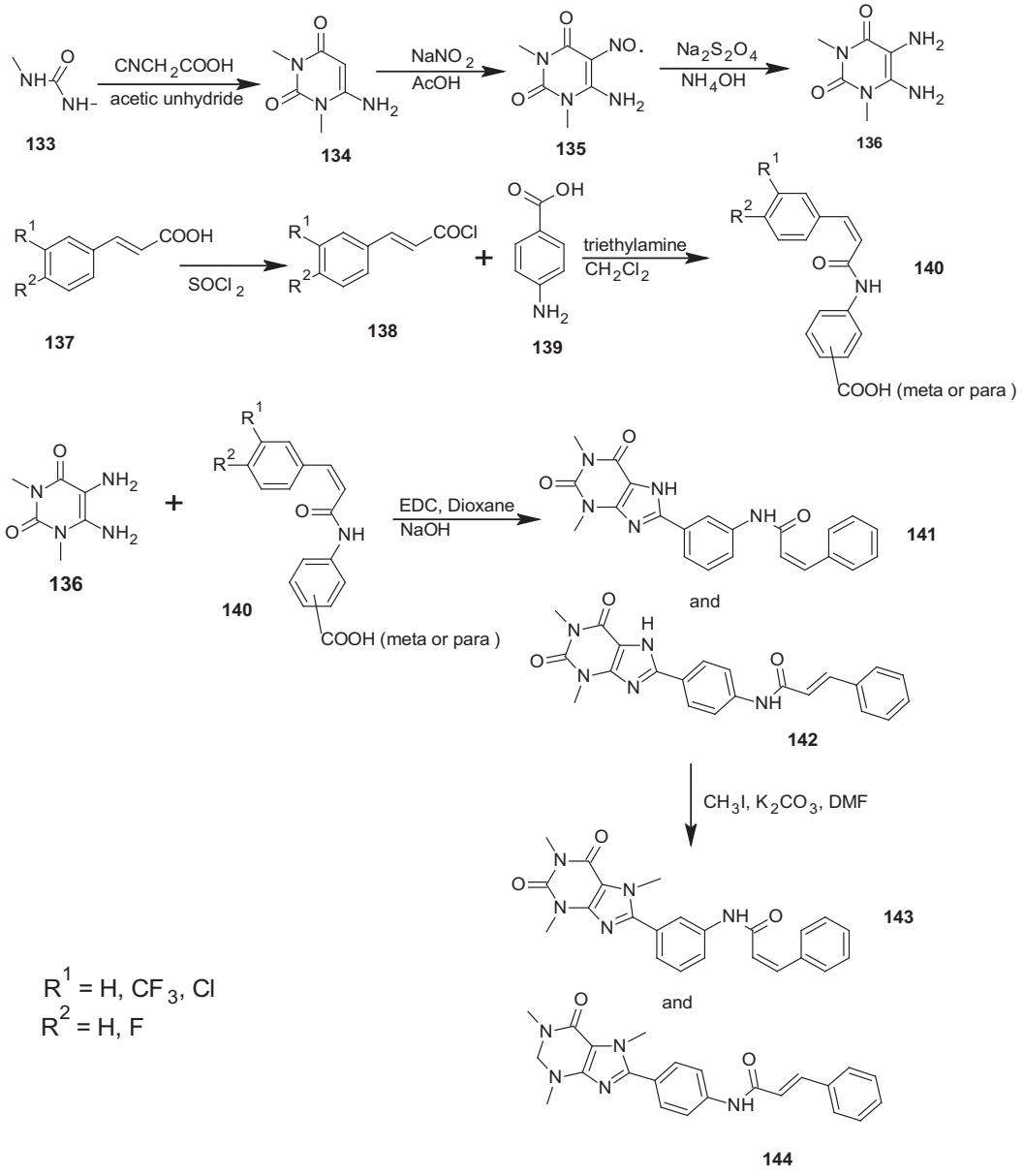
2.8. Thiazole as MAO inhibitor

A large series of (hetero) arylidene-(4-substituted-thiazol-2-yl) hydrazine derivatives **197** (Scheme 35) have been recently reported (Daniela et al., 2012). Substituted carbonyl compounds **194** treated with thiosemicarbazide afforded semicarbazone which on treatment with α-halo substituted acetophenone resulted in desired derivatives.

The synthesis of compounds **202** has been achieved by the reaction of cycloalkyl thiosemicarbazones **200** with ω-bromoacetophenone **201** (Scheme 36). Similarly, aryl substituted thiazole derivatives were synthesized via the condensation of arylthiosemicarbazones with α-haloketones (Chimenti et al., 2007).

A similar reaction sequence (Scheme 37) was used for the synthesis of a series of 2-methylcyclohexylidene-(4-arylthiazol-2-yl) hydrazones (Chimenti et al., 2008b). Compounds **203** reacted directly with thiosemicarbazide, resulted in formation of corresponding thiosemicarbazones which subsequently on treatment with α-haloketones afforded 4-substituted thiazole derivatives **206.**

A huge series of (4-aryl-thiazol-2-yl) hydrazones have been reported (Chimenti et al., 2010b). Appropriately



Scheme 24

substituted carbonyl reacted directly with thiosemicarbazide, and the obtained thiosemicarbazones were subsequently converted into required derivatives **211** by the Hantzsch reaction with 2 or 2, 4-substituted α-bromoacetophenones (Scheme 38).

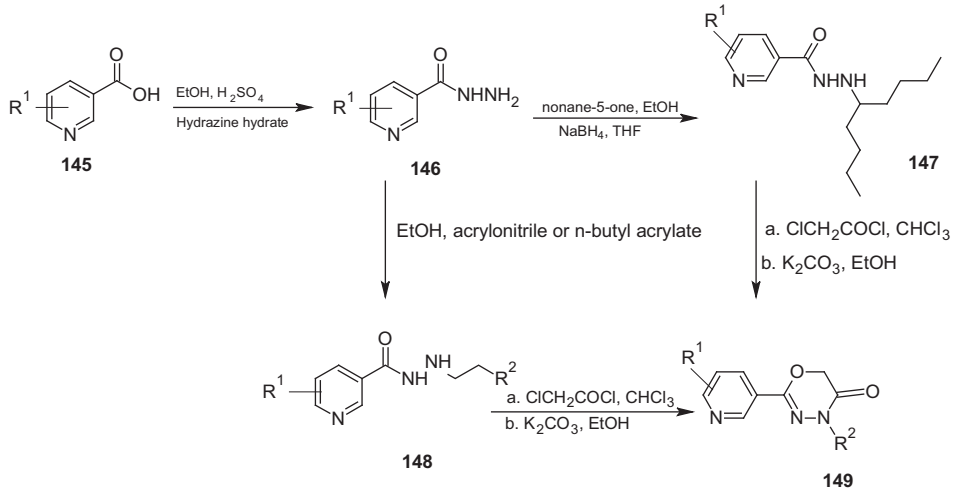
Synthesis of 2, 4-disubstituted thiazole compounds **216** (Scheme 39) has been reported (Chimenti et al., 2009). The hybrid derivatives of coumarin-thiazole were achieved by the Hantzsch reaction of appropriate thiosemicarbazones and 3-α-bromoacetyl coumarin.

An immense series of (4,5-substituted-thiazol-2-yl) hydrazone compounds (Scheme 40) has been reported (Chimenti et al., 2010c).

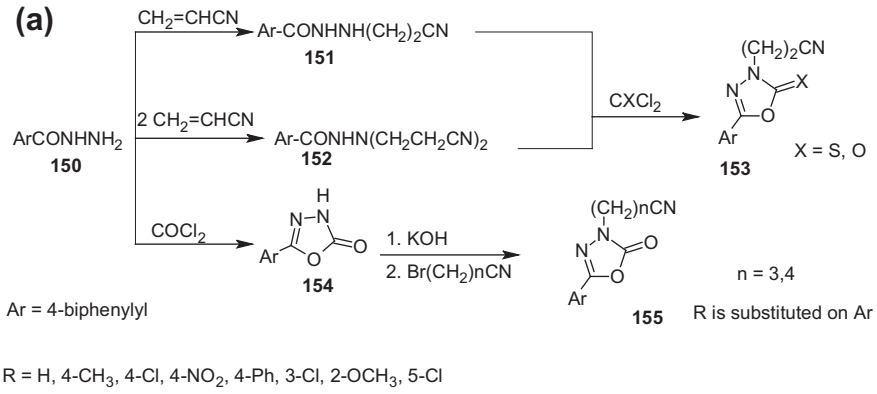
Few novel 1-(4-arylthiazol-2-yl)-2-(3-methylcyclohexylidene) hydrazine (Scheme 41) derivatives had been synthesized (Chimenti et al., 2010d). The thiosemicarbazones of 3-methylcyclohexanone condensed with substituted α-haloacetophenone and afforded corresponding thiazole derivatives **229** via the Hantzsch reaction.

Recently, halogenated derivatives of 1-aryliden-2-(4-phenylthiazol-2-yl) hydrazines (Scheme 42) have been appeared (Distinto et al., 2012). The appropriate aryl aldehydes **230** react with thiosemicarbazide **231** and the obtained thiosemicarbazones treated with halogen substituted acetophenone **233** gave desired derivatives **234**.

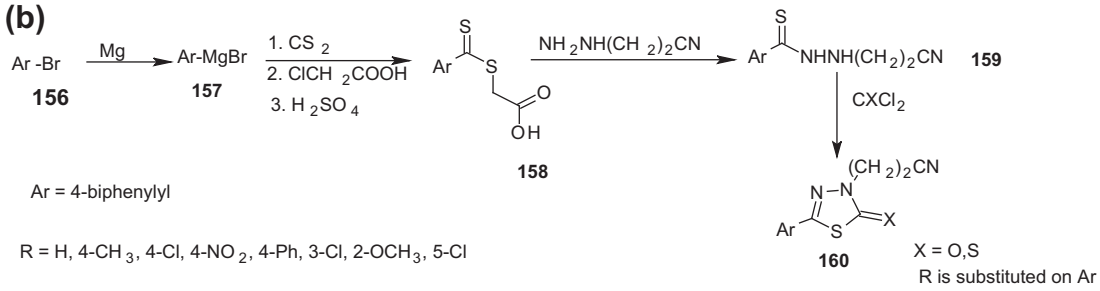
A new series of [4-(3-methoxyphenyl)-thiazol-2-yl] hydrazine derivatives **238** (Chimenti et al., 2010e) were synthesized (Scheme 43). Nucleophilic addition of thiosemicarbazide with different carbonyl compounds formed thiosemicarbazones and were subsequently converted into thiazolyl hydrazines by 3-methoxyphenyl acyl bromide in DMF. Synthesis of **240** has been achieved by halogenations of 3-methoxy acetophenone with bromine in chloroform. Most of the compounds were found to be selective towards MAO-B enzyme.



Scheme 25



Scheme 26a

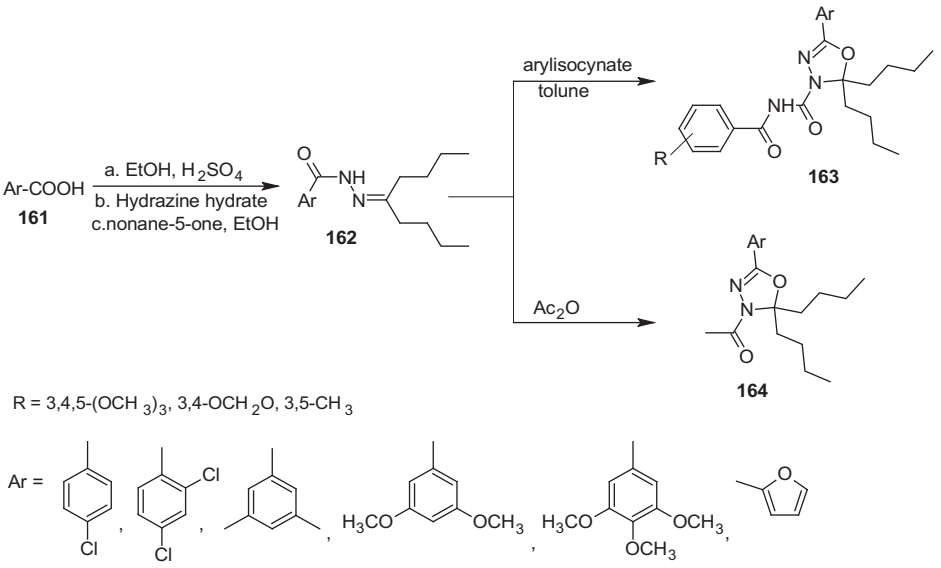


Scheme 26b

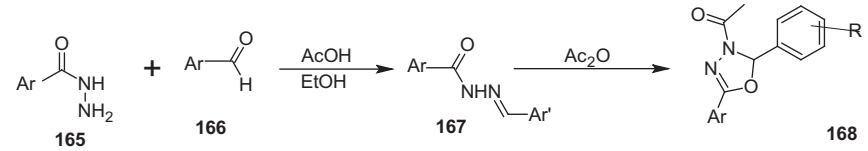
3. Other nitrogen heterocycles as MAO inhibitor

3.1. Piperine

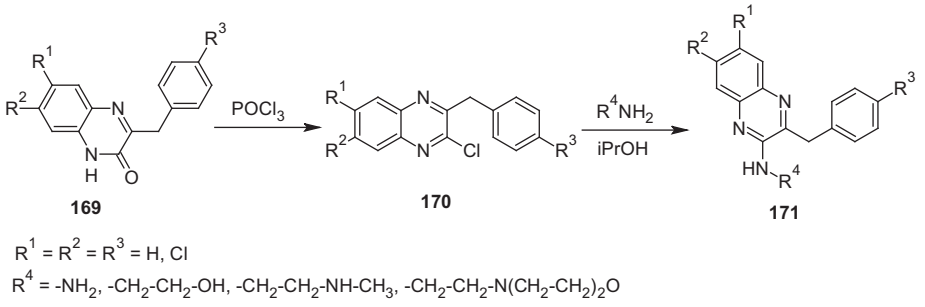
A series of piperine derivatives (Mu et al., 2012) have been prepared (Schemes 44a and 44b). It was worth to note that most of the small amine moieties substituted on the piperidine ring proved to be potent and selective inhibitors of MAO-B rather than of MAO-A. Piperinic acid was obtained by alkaline hydrolysis of piperine. The amides **243** were obtained from the corresponding carboxylic acids through acyl chloride formation with appropriate amines. The diacetyl phenyl containing analogue **249** was prepared by the reaction of piperine with boron tribromide (BBr_3) and acetic anhydride, while **250** was



Scheme 27



Scheme 28

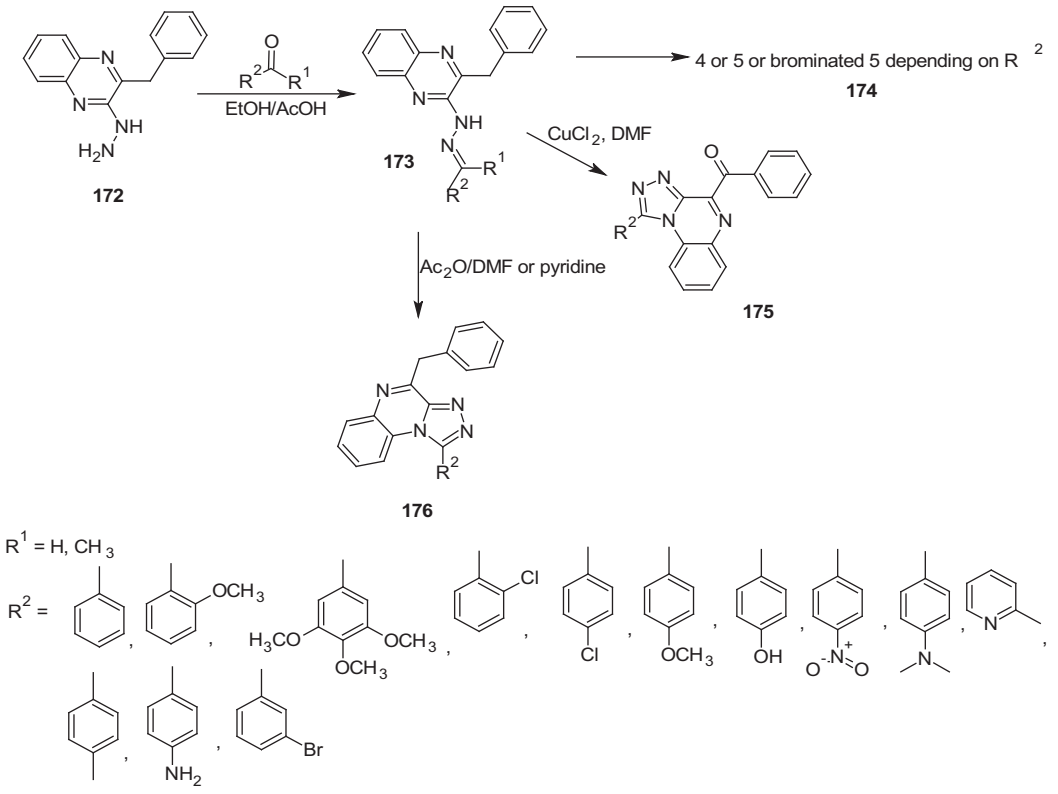


Scheme 29

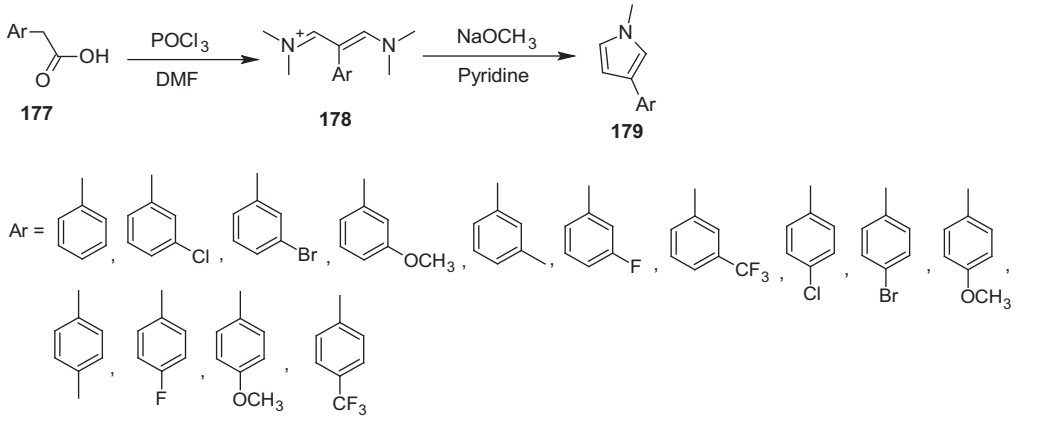
obtained by the reduction of piperine using $NaBH_4$ in THF. The compounds **251** were subjected to hydrogenation yielded corresponding saturated analogues **252**.

3.2. Morpholine

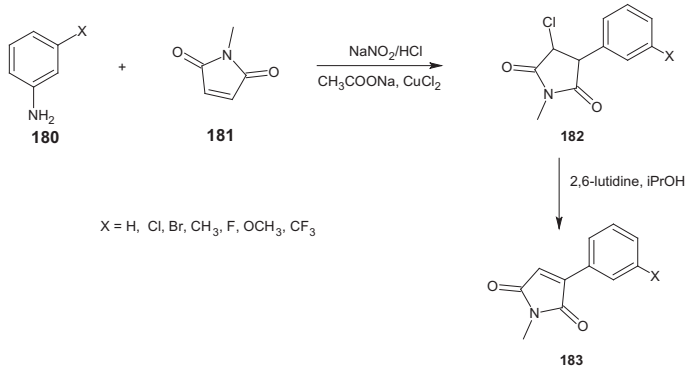
Synthesis of (±) 2-aryl thiomorpholine and (±) -2-aryl-thiomorpholine-5-one (Luhr et al., 2010) has been accomplished (Scheme 45). Condensation of appropriately substituted aromatic aldehydes with nitromethane by Henry–Knovenagel condensation followed by Michael addition of methyl thioglycolate to the nitro styrenes afforded corresponding nitro esters. Finally, compounds **256** were synthesized by a nucleophilic attack on the ester group of the amine obtained by the reduction of a nitro group with zinc. Reduction of the lactum with diisobutylaluminium hydride (DIBAL-H) yielded



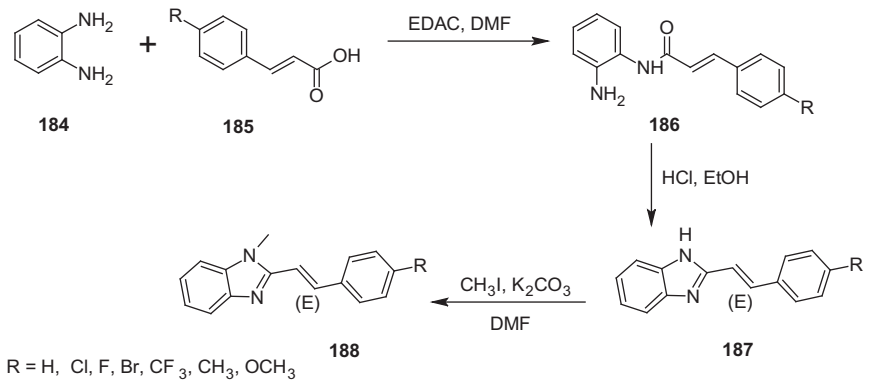
Scheme 30



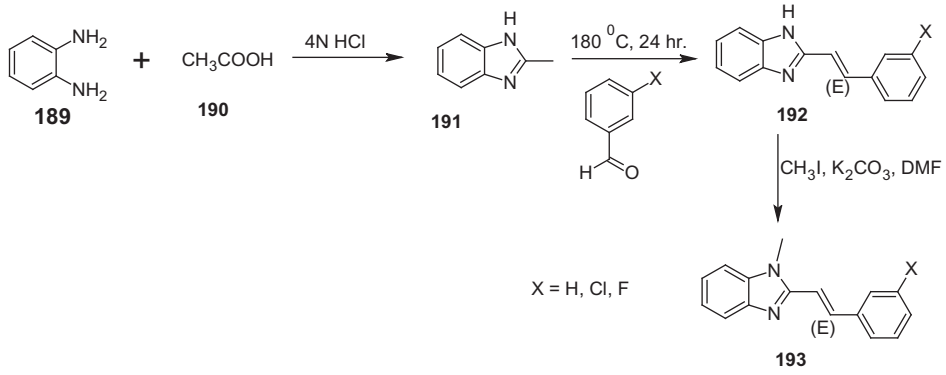
Scheme 31



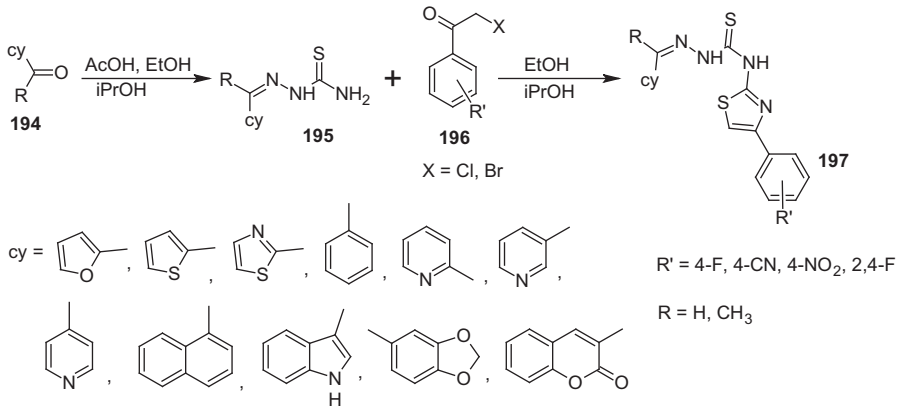
Scheme 32



Scheme 33



Scheme 34



Scheme 35

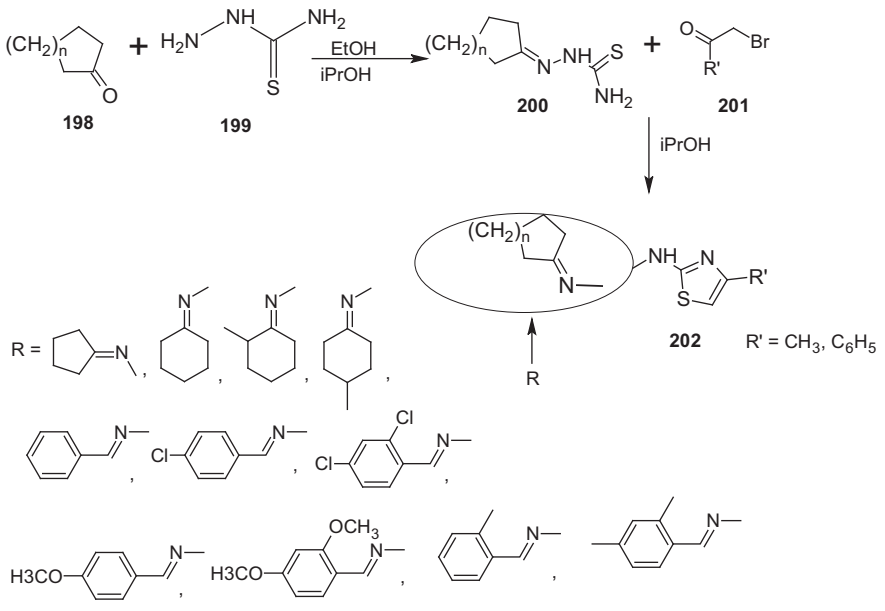
desired thiomorpholine derivative **257**. All the synthesized compounds were found to be selective MAO-B inhibitors.

3.3. Imidazoline

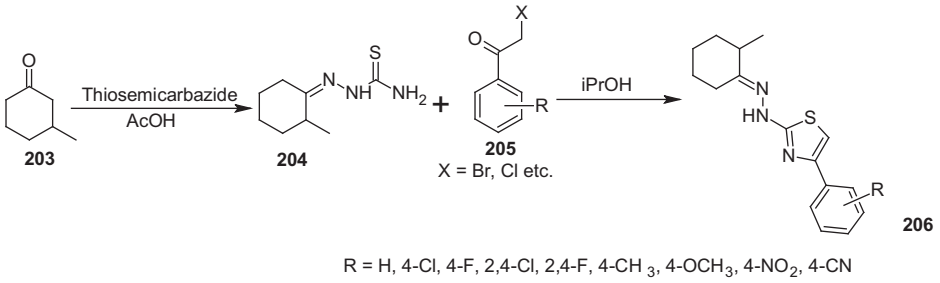
A facile, ultrasound mediated synthesis (Anna et al., 2009) of 2-imidazoline derivatives **260** in water has been achieved by the condensation of aldehydes and ethylenediamine in the presence of N-bromosuccinimide (NBS) (Scheme 46). Some of them showed potent and selective MAO inhibitory activity, especially for the MAO-B isoform.

3.4. Heterocyclic substituted propargylamines

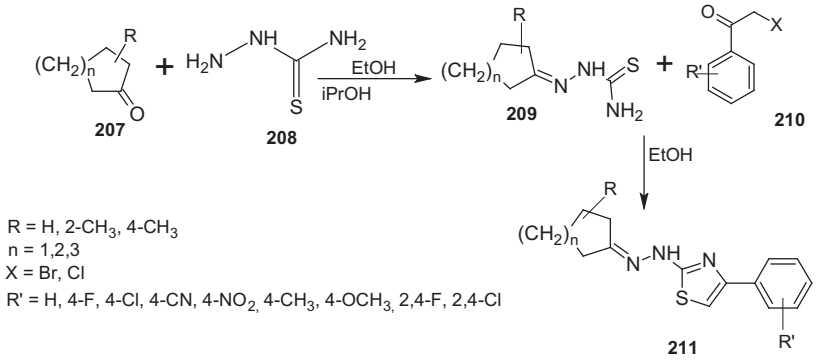
Recently, a series of hetero cyclic substituted alkyl and cyclo alkyl propargylamines (Schemes 47a and 47b) have been prepared



Scheme 36



Scheme 37

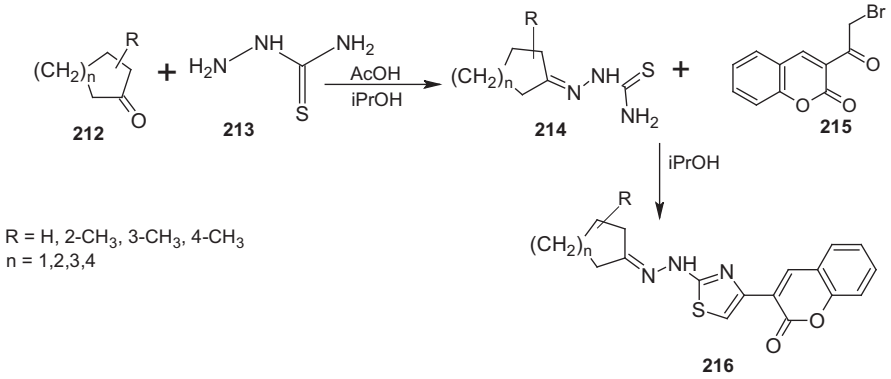


Scheme 38

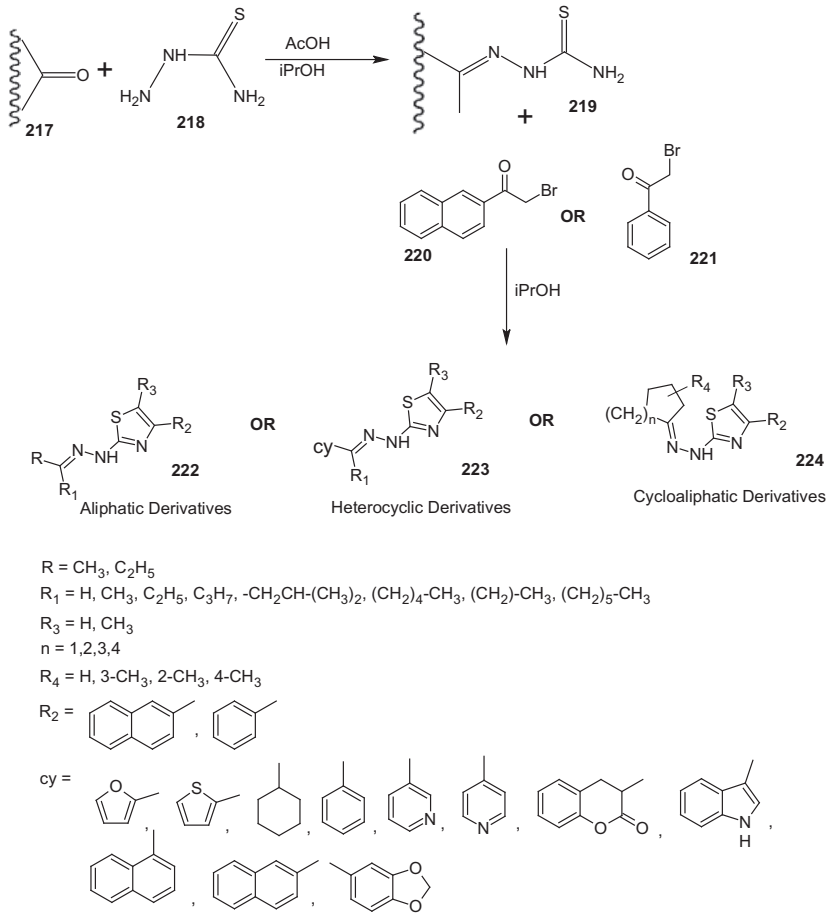
with MAO-B inhibitory activity (Samadi et al., 2012). Initially, 2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydrobenzo-[1,6]-naphthyridine-10-amine **262** was synthesized from 2-aminobenzonitrile (Friedlander type reaction) and 1-(prop-2-yn-1-yl)-piperidine-4-one. Similarly, the compounds **264** (Scheme 47b) were prepared from 2-aminopyridine-3-carbonitriles.

3.5. Indeno pyridazine

Synthesis of 3,8-disubstituted-*5H*-indeno [1,2-c]-pyridazin-5-one derivatives **270** (Reniers et al., 2011a,b) has been achieved (Scheme 48). All compounds showed higher activity and selectivity against MAO-B enzyme. Initially, 5-hydroxy-1-indenone



Scheme 39

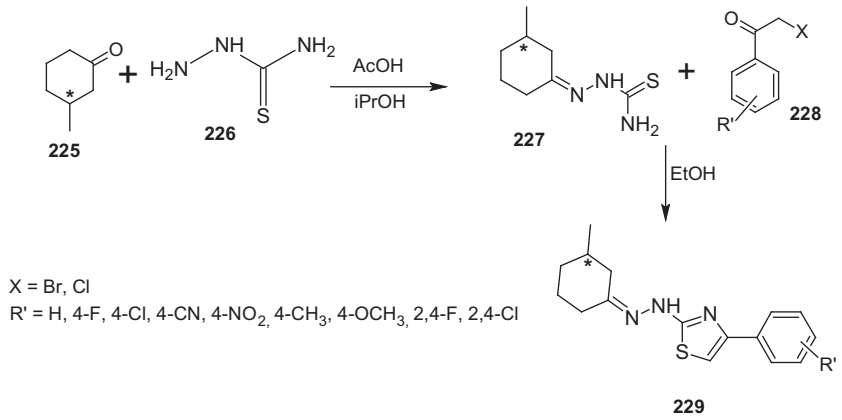


Scheme 40

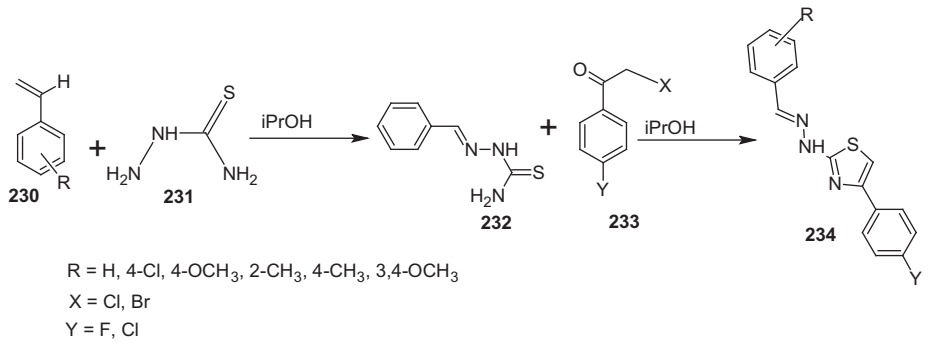
reacted with 1-tosyl-4,4,4-trifluorobutane afforded **266** which on oxidation with selenium dioxide (SiO_2) followed by Aldol formation; by the reaction between **267** and (trifluoromethyl) acetophenone in acetic acid. Subsequently, **269** reacted with hydrazine hydrate in acetic acid and afforded desired derivatives.

3.6. Quinoline

Recently (Chaurasiya et al., 2012), 5-phenoxy analogues of primaquine as potential MAO-A inhibitors have been synthesized according to protocol (Scheme 49). Appropriate halogenated phenol was coupled with N-(5-chloro-4-methoxy-2-nitrophenyl) acetamide to afford diphenyl ethers which on hydrolysis produces aniline hydrochlorides, which were condensed with methyl vinyl ketone to give nitro quinoline intermediates. Catalytic hydrogenation of the nitro quinoline and subsequent attachment of a side chain 4-oxo-1-phthalamide-opentane, afforded primary amine protected 8-aminoquinolines. Deprotection of the terminal amine and treatment of the resulting amines with the succinic acid gave compounds **279.**



Scheme 41



Scheme 42

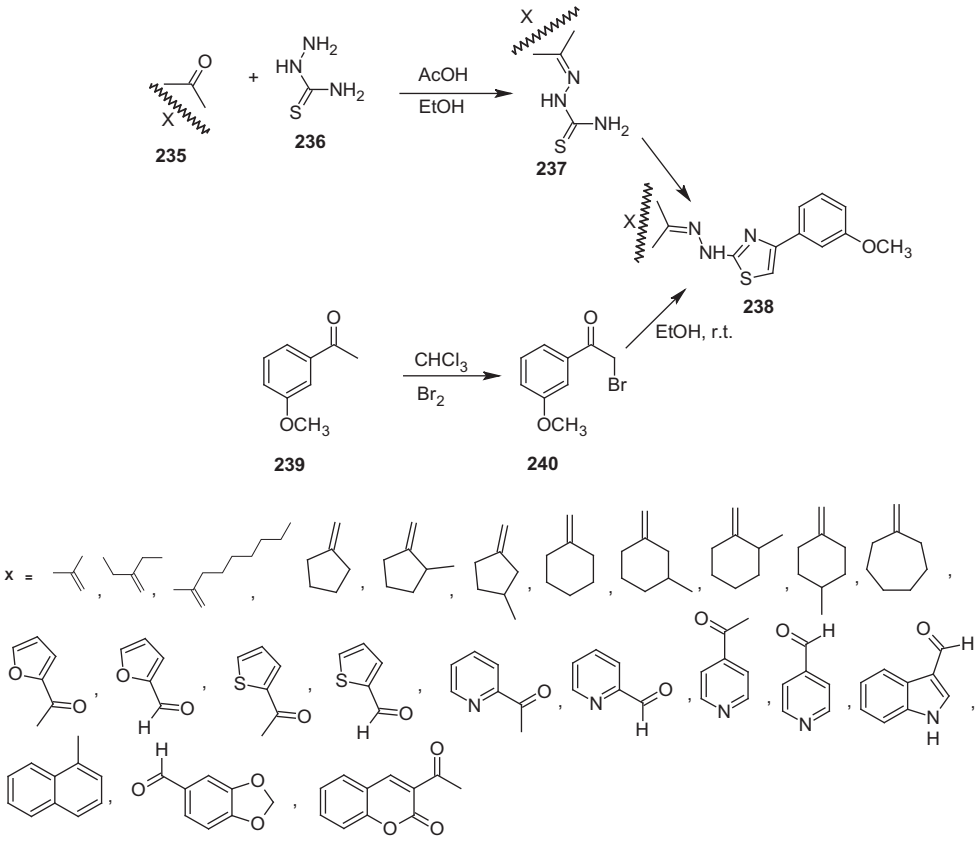
3.7. Pteridine

Synthesis of pteridine-2,4-dione derivatives **283** has been achieved (Prins et al., 2009). The key starting material, 1,3-dimethyl-5,6-diaminouracil was reacted with the appropriate aldehyde to yield the pyrimidines. The pyrimidines were cyclized by the addition of triethyl ortho formate, yielded pteridine-2,4-diones (Scheme 50). The compounds were found to have a promising MAO-B activity.

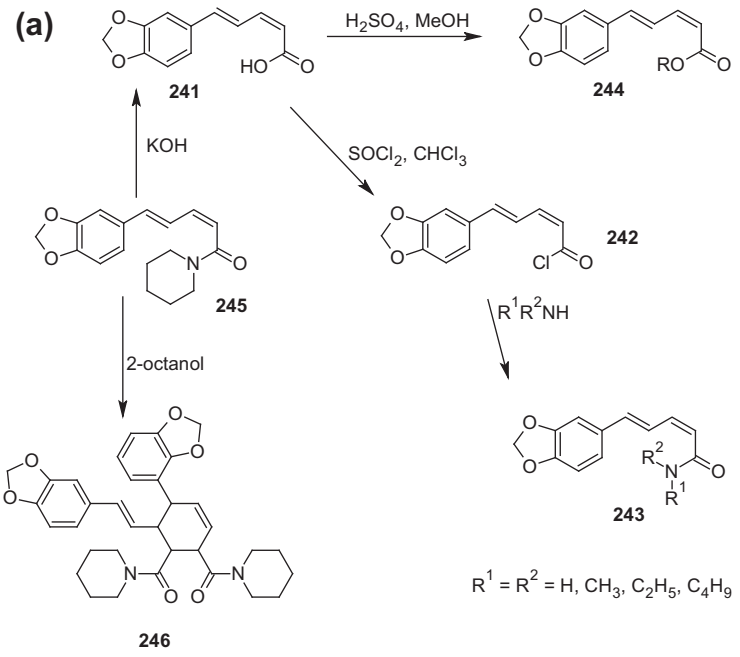
4. Conclusion

Salient findings related to chemical structures and the bioactivities of Nitrogen Heterocycles as MAO inhibitors are,

- Substitution of phenyl, acetyl and thiocarbamoyl at N^1 of pyrazoline leads to selectivity towards MAO inhibition and elongation of the N^1 chain decreases the activity against MAO-B than acetyl due to the formation of unstable complex.
- Presence of a ring at nitrogen of amide, thioamide and semicarbazide in pyrazoline series, increases potency as well as selectivity towards MAO-A, however, its absence equally decreases potency and selectivity towards MAO-A and MAO-B.
- Substitution of toluene sulphonyl derivative at N^1 position with 2-hydroxyphenyl at C3 and 2,4-dihydroxyphenyl ring at C5 of pyrazoline provides the most active and selective MAO-A inhibitor.
- Compounds, 3, 5-diphenyl pyrazoline with an anthracene moiety at C3 and substitution of methoxy or nitro group at the para position of phenyl at C5 increase activity and selectivity towards MAO-B.
- In 3,5-diaryl-1-carboxamide pyrazoline series substitution of the 4-hydroxy group on a phenyl at C3 increases the potency towards MAO. At the same time replacement of aryl at C5 by a five-member hetero aromatic ring also increases the potency towards MAO. In the same series derivatives with a 4-chlorophenyl substituent at C5 position shows high activity against both MAO-A and MAO-B but with opposite selectivity, i.e. a derivative with methyl and fluoro group at para position of C4 phenyl showed selectivity towards MAO-A and MAO-B respectively.
- In the prenylated series of pyrazolines bearing acetyl or carbazide at N^1 position the compounds with benzyloxy group and chlorine at para position at C5 increases MAO-B potency while methyl and methoxy groups in the same position decreases MAO-B inhibition.
- Substitution at C8 of caffeine with an electron deficient group (styryl) produces higher affinity towards MAO-B and it was supported by the fact that saturation of double bond of styryl resulted in a decrease in MAO inhibitory activity. The E isomers of styryl xanthine as well as styryl benzimidazole derivatives were active inhibitors than Z isomers.
- In the case of styryl xanthinyl series, caffeine was found to be a very weak inhibitor of MAO-B while 8 substituted analogues were potent MAO-B inhibitors. Replacement of



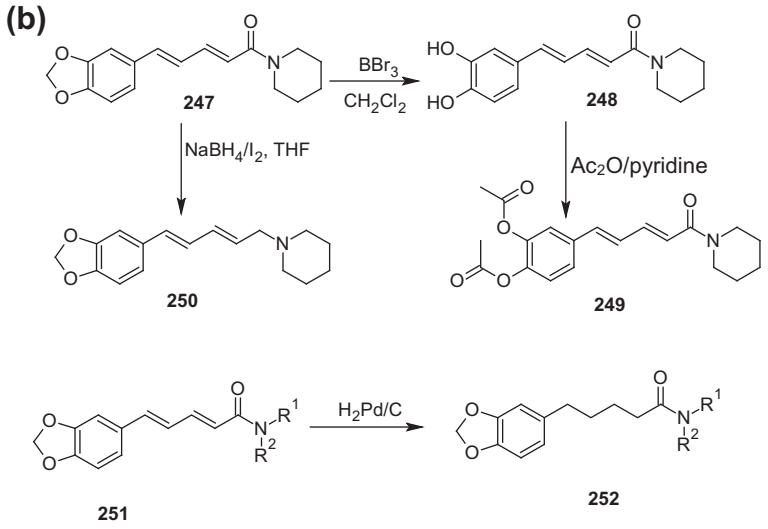
Scheme 43



Scheme 44a

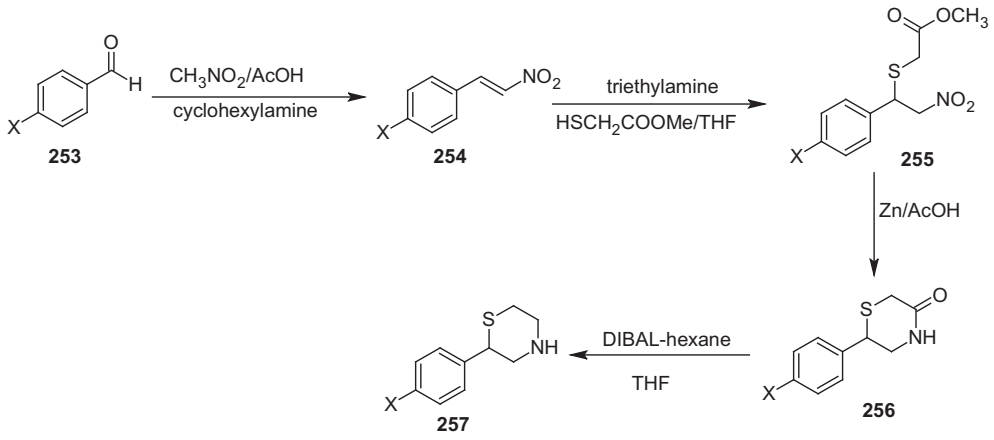
1, 3-dimethyl groups of the xanthinyl moiety with ethyl groups decreases the potency of MAO-B inhibition. Similarly 7-N-methylxanthine compounds were more potent inhibitors than the corresponding 7*H*-xanthine analogues.

- The introduction of a styrol-formamide group in 8-phenyl xanthine at position 3 may enhance activity and selectivity on MAO-B inhibition and substitution of fluoro on the same compounds increases the selectivity towards MAO-B.



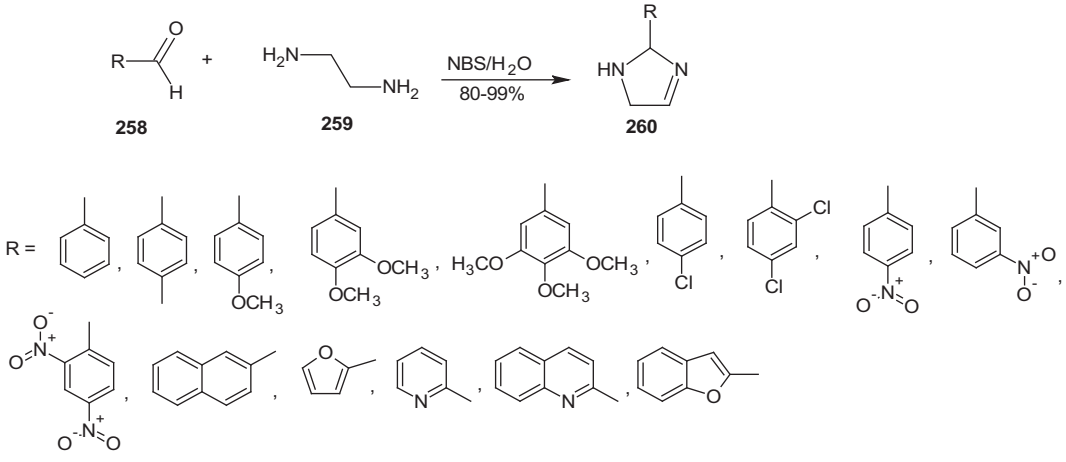
$R_1 = R_2 = H, CH_3, C_2H_5, C_4H_9$

Scheme 44b

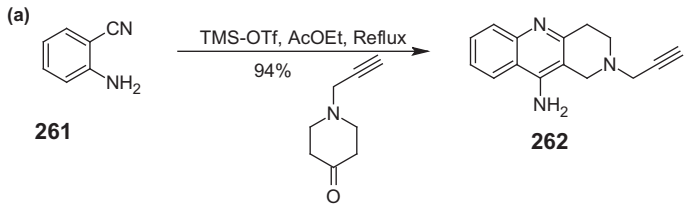


X = H,-OCH_3, CH_3CH_2O, $CH_3CH_2CH_2O$, $CH_3CH_2CH_2CH_2O$, $PhCH_2O$

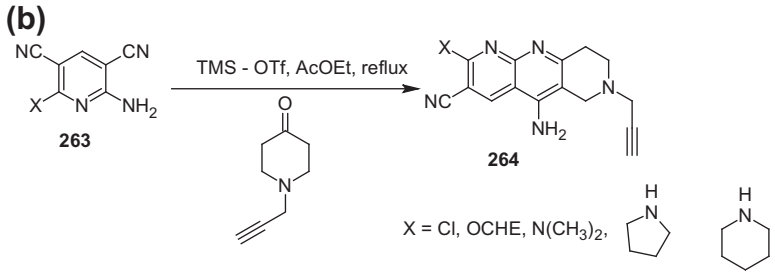
Scheme 45



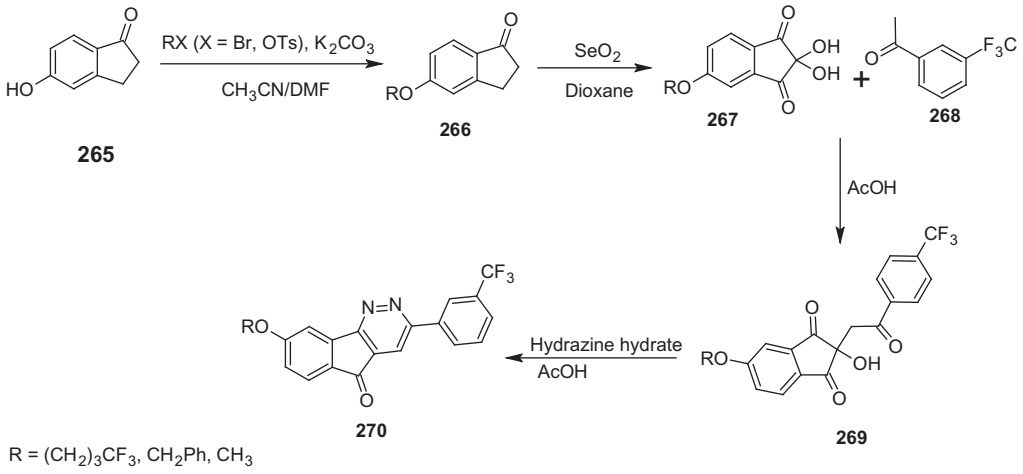
Scheme 46



Scheme 47a

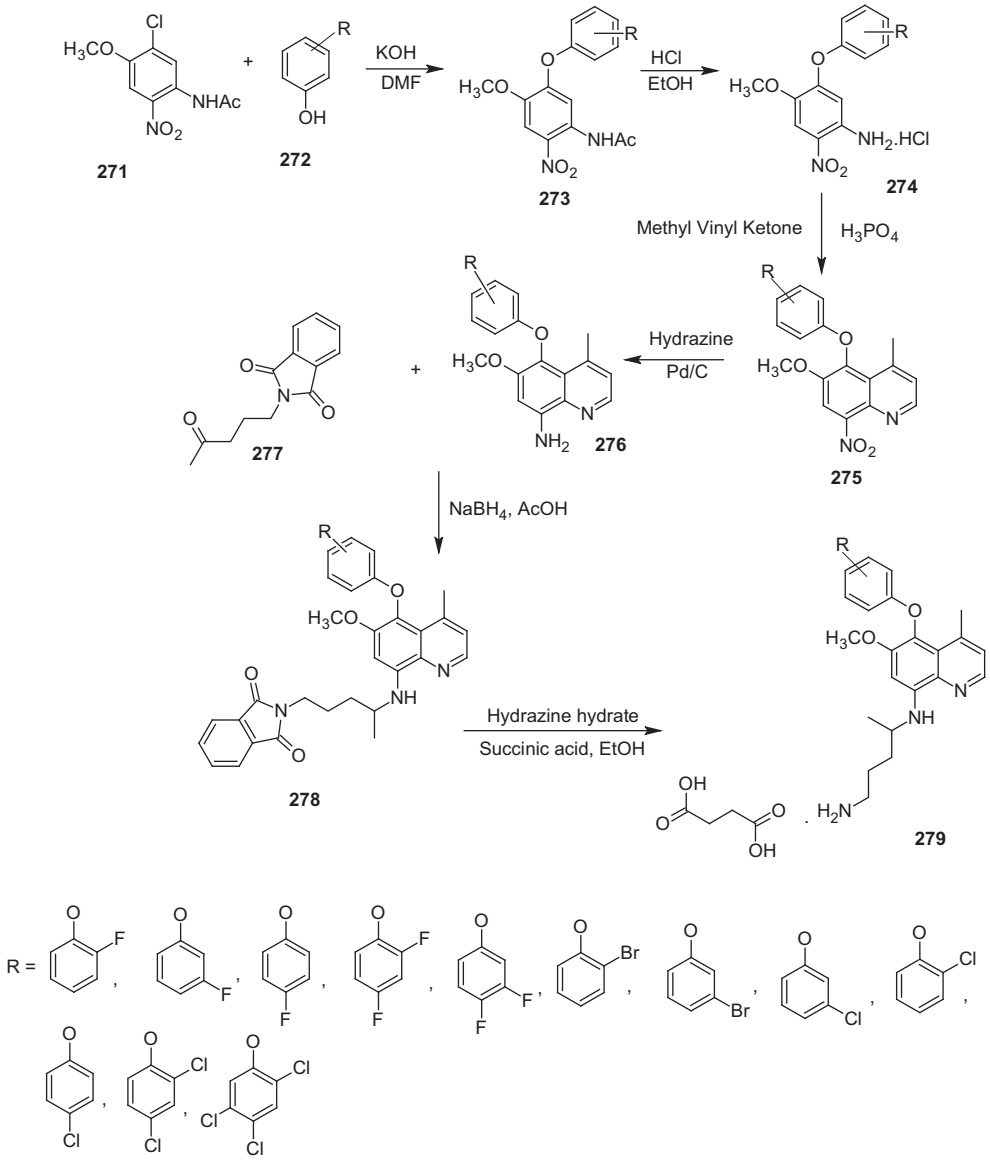


Scheme 47b

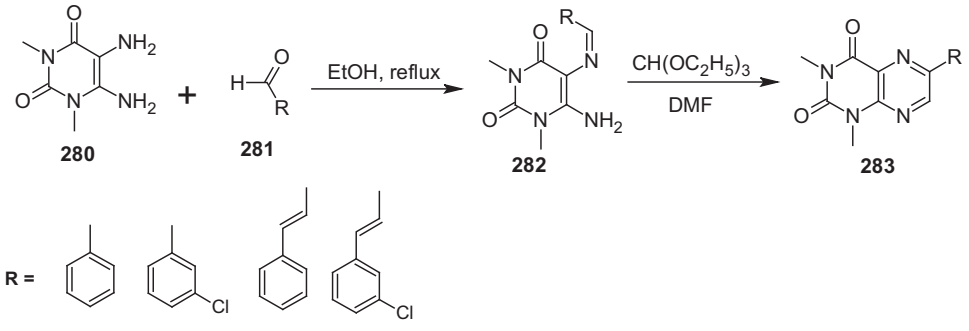


Scheme 48

- In 8-(benzamido)-phenyl linked to xanthine ring, compounds with smaller groups were more potent MAO-B inhibitors. The diaryl amide in comparison with styrenes can enhance MAO-B inhibition.
- In styryl benzimidazole series (E)-1-methyl-styrylbenzimidazole analogues were more potent MAO inhibitors than their corresponding *1H* analogues and substitution of 3-Cl and 3-F on the same, leads to more potent compounds. Moreover, 3,4-dichlorostyryl caffeine was most potent than others from the series.
- Compounds 3-benzoyl-2-substituted quinoxalines were found to be selective MAO-A inhibitors.
- In 5-aryl-1,3,4-oxadiazol-2(*3H*)one series with cyanoethyl group present at 3 position, substitution of electron donating group at the para position of aryl (H, Me, OMe) ring increases selectivity towards MAO-A whereas electron withdrawing group (NO_2) or a hydrophobic biphenyl group increases the selectivity towards MAO-B.
- A cyanoethyl group in all the mentioned series of oxadiazole was essential for MAO inhibition; because decrease in activity and selectivity of inhibitors towards MAO were observed with the increase of the length of the cyano alkyl chain in 3 position. Oxadiazolones were found to be more active and selective than oxadiazinones.
- In 1,3,4-oxadiazin -5-(6*H*)one derivatives containing hydrophobic group at the position C2 and long chain at position N^4 resulted in potent and selective compounds against MAO.
- The derivatives with 3-acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazole were considered as a promising scaffold for the design of selective MAO-B inhibitor. The R enantiomer of these compounds was significantly active and selective in comparison to racemic mixture, while S enantiomer was inactive. The introduction of 4-chlorophenyl on position 2 of dihydro-1,3,4-oxadiazole increases activity and selectivity towards MAO-B.



Scheme 49



Scheme 50

- In a series of halogenated indolylimidazolidin-4-one derivatives, multiple N-methylations of the imidazolidinone moiety, one of which should be the methylation of N^2 in addition to either N^3 or N^4 along with bromination at position 5 or 6 are important for MAO-A potency and selectivity.

- Introduction of a bulky substituent (benzyloxy) at position 5 of indole increases potency and selectivity for the MAO-B isoform. In 5-benzamidoindolyl series substitution of Cl at the para position of phenyl ring at C5 position of indole enhances both MAO-A and MAO-B inhibition potencies, since the unsubstituted compounds were less potent MAO inhibitor.
- In the mentioned series of 1-(4-substituted-thiazol-2-yl)-2-(alkyl/cycloalkyl/aryl)-hydrazines, the best substituent on the aromatic ring at position 4 of the thiazole nucleus was electron withdrawing groups (NO_2, Cl, CN, F) while the introduction of more steric hindered naphthalene or coumarin rings at the same position of thiazole nucleus or the presence of methyl at C5 led to decreased MAO inhibitory activity. The R enantiomer was the most selective MAO inhibitor from the series.
- In the (thiazol-2-yl)-hydrazine compounds, presence of smaller heterocyclic moieties on the N^1 hydrazine was important for MAO activity and selectivity because a bulkier substitution including aryl ring at N^1 resulted in the loss of MAO inhibitory activity and selectivity. Replacement of hydrogen by methyl group at α-carbon to the N^1 hydrazine moiety increases the ability of compounds to inhibit MAO-B.
- A compound bearing naphthalene moiety on C4 of the scaffold (4,5-substituted-thiazol-2-yl)-hydrazones possessed a greater inhibitory activity on MAO-A and MAO-B than the compound bearing less substituent at C4 of thiazole, and a CH_3 group on C5 and is probably because of the steric hindrance of methyl group on C5 of the thiazole.
- Elongation of the alkyl chain on hydrazone nitrogen (C2 of thiazole nucleus) produces a slight reduction in MAO inhibition but increases selectivity. On the other hand, carbocyclic derivatives showed loss of MAO inhibition activity when the ring dimension was increased.
- In 1-(4-arylthiazol-2-yl)-2-(3-methylcyclohexylidene)-hydrazines, it was observed that racemic compounds with 4-Cl, 4-CH_3, and 4-OCH_3 substituted phenyl group or an unsubstituted C4 position of thiazole ring displays MAO inhibitory activity with selectivity towards MAO-B.

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