LITERATURE REVIEW

Heterocycles form by far the major of classical divisions of organic chemistry and are of immense use biologically and industrially. It is well known that the heterocycles are present in all kinds of organic compounds of interest in biology, pharmacology, material sciences, electronics, optics, and so on. Heterocyclic nucleus imparts an important function in medicinal chemistry and serves as a key template for the development of various therapeutic agents [Kashyap *et al.* 2011]. Mostly researchers have maintained their interest in sulfur and nitrogen-containing heterocyclic compounds through decades of historical development of organic synthesis [Valverde and Torroba 2005] but heterocycles with other heteroatoms such as oxygen [Liu 2001], phosphorus [Reddy *et al.* 2004] and selenium [Abdel-Hafez 2008] also appears.

Majority of clinically used drugs possess a heterocyclic moiety in their structure. There are widespread therapeutic uses of synthetic heterocycles such as antibacterial, antimycobacterial, trypanocidal, anti-HIV, genotoxic, herbicidal, analgesic, antiinflammatory, muscle relaxants, antileishmanial, anticonvulsant, anticancer, antimalarial, antifungal, antitubercular, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents [Mittal 2009; Nagalakshmi 2008; Nekrasov 2001; Sperry and Wright 2005; Polshettiwar and Varma 2008; Katritzky 1992]. The exploration for new biologically active heterocyclic analogues continues to be an area of intensive research in medicinal chemistry.

Since our research work is focused on hydrazone and semicarbazone scaffolds bearing benzothiazole, thiazole, benzodioxole and isatin residues; the chemical and biological reviews of these classes are presented here.

2.1. REVIEW ON HYDRAZONES

Hydrazones and their analogs constitute a versatile class of compounds in organic chemistry. These compounds were found to possess interesting biological properties which includes anticonvulsant, analgesic, antiinflammatory, antiplatelet, antimalarial, antimicrobial [Rollas and Kucukguzel 2007], antimycobacterial [Mao *et al.* 2007], antitumor [Noulsri *et al.* 2009; Andreani *et al.* 2008; Vicini *et al.* 2006], anti-HIV

activity besides having anti-depressant [Singh *et al.* 1992] MAO-A and MAO-B inhibitory activity [Bernard *et al.* 1995] (**Figure 2.1.**).

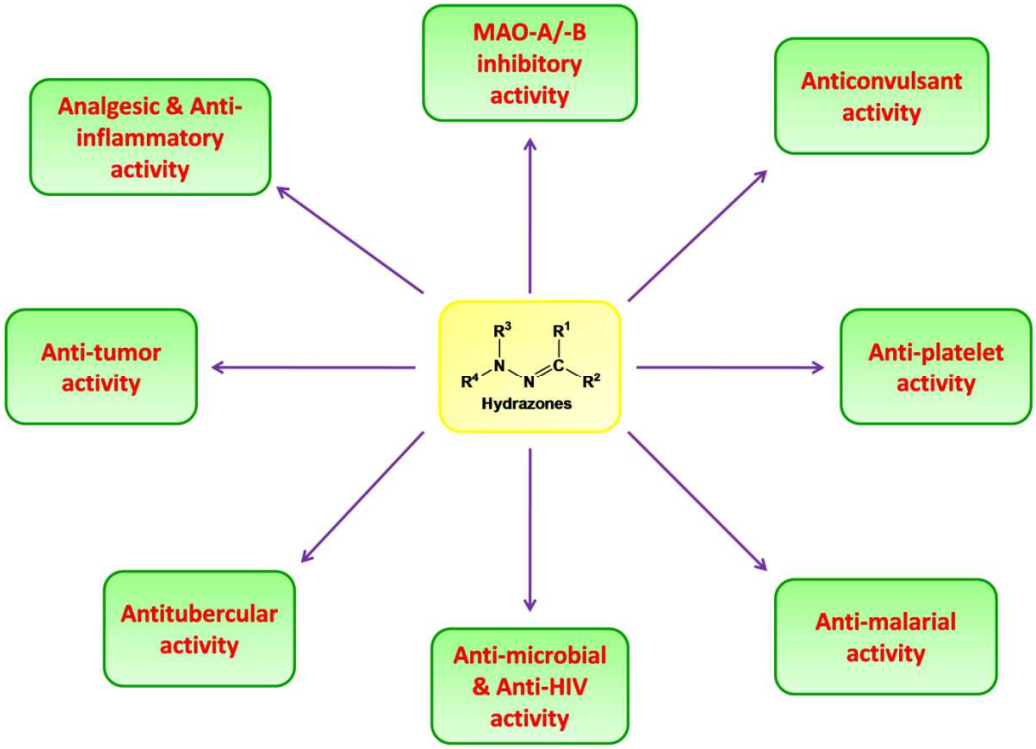


Figure 2.1. Various biological actions of hydrazones

2.1.1. Chemical review on hydrazones

Hydrazones are important scaffolds for drug design. They act as possible ligands for metal complexes, organocatalysis and also for the synthesis of various medicinally important heterocyclic compounds [Barbazan *et al.* 2008; Banerjee *et al.* 2009; Ghavtadze *et al.* 2008; Inamoto *et al.* 2007; Dang *et al.* 2007; Sridharan *et al.* 2007; Colotta *et al.* 2007; Filak *et al.* 2008; El-Gendy *et al.* 2008; Huang *et al.* 2009]. The most desirable characteristics of hydrazones include the ease of preparation, increased hydrolytic stability relative to imines, and tendency toward crystallinity. Because of these positive traits, hydrazones have been under study for a long time, but much of their basic chemistry still remains to be explored.

Hydrazones contain two nitrogen atoms adjacent to each other but of different nature and a C-N double bond that is conjugated with a lone electron pair of the terminal nitrogen atom. These structural fragments are mainly responsible for the physical and chemical

properties of hydrazones. Both nitrogen atoms of the hydrazone group are nucleophilic, although the amino type nitrogen is more reactive. The carbon atom of hydrazone group has both electrophilic and nucleophilic character (**Figure 2.2.)** [Kim and Yoon 2004; Brehme *et al.* 2007].

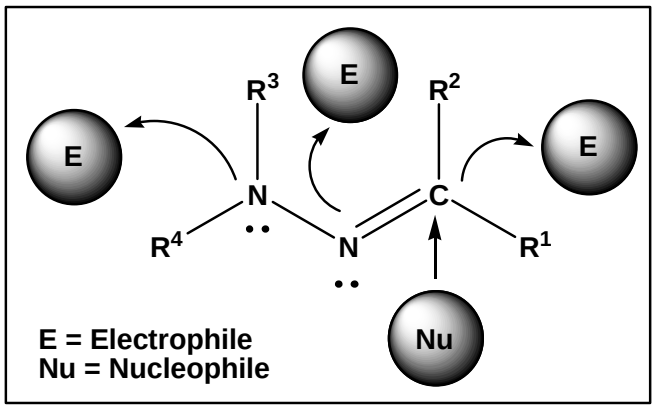


Figure 2.2. Reactive centers of hydrazones

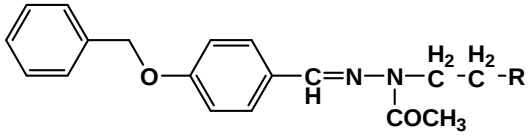
Due to the ability of hydrazones to react with electrophilic and nucleophilic reagents, they are widely used in organic synthesis, especially for the preparation of heterocyclic compounds [Kim and Yoon 2004; Rollas and Kucukguzel 2007; Martin-Zamora *et al.*, 2004; Deng and Mani 2008].

2.1.2. Biological review on hydrazones

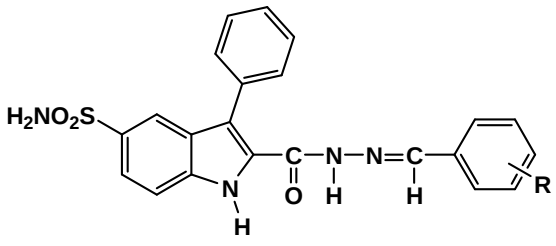
2.1.2.1. CNS activities

2.1.2.1.1. MAO inhibitory activity

In the past [Weinswig and Roche, 1965; Pignatello *et al.*, 1994], some monosubstituted hydrazones were reported as non-specific but potent MAO inhibitors.



1 (R = CN), **2** (R = OH)



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Bernard *et al.*, synthesized substituted acylhydrazones of various aromatic aldehydes and 4-(benzyloxy)acetophenone and evaluated for the monoamine oxidase A and B inhibitory activities . The compounds **1** and **2** were found to be most potent, very specific and

reversible inhibitors of MAO-B with the IC_{50} values of 3 nM and 6.3 nM respectively [Bernard *et al.* 1995].

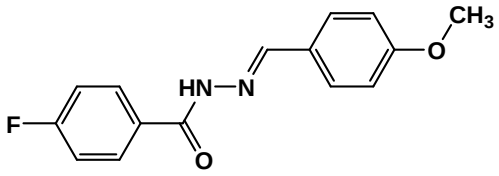
2.1.2.1.2. Antidepressant activity

Iproniazide, isocarboxazide and nialamide, which are hydrazide derivatives, exert their action by inhibiting the enzyme monoamine oxidase (MAO). There have been many reports on the antidepressant/MAO-inhibiting activity of hydrazones derived from substituted hydrazides and reduction products.

Ten new arylidenehydrazides **3** were synthesized by reacting 3-phenyl-5-sulfonamidoindole-2-carboxylic acid hydrazide with various aldehydes and evaluated for their antidepressant activity. 3-Phenyl-5-sulfonamidoindole-2-carboxylic acid-3,4-methylenedioxy/4-methyl/4-nitrobenzylidene-hydrazide showed antidepressant activity at 100 mg/kg [Ergenc and Gunay 1998].

2.1.2.1.3. AChE inhibitory activity

Mohsen *et al.*, synthesized a series of hydrazide-hydrazone derivatives and evaluated them for their ability to inhibit AChE. Among the tested compounds, 4-fluorobenzoic acid [(4-methoxyphenyl)methylene] hydrazide **4** and 2-[(fluorobenzoyl)hydrazono]-1,3-dihydro-indol-3-one **5**, showed noteworthy anti-AChE activity when compared to standard drug donepezil [Mohsen *et al.* 2015].



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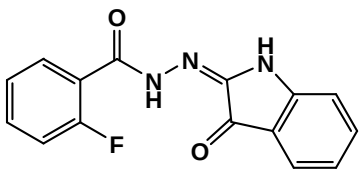

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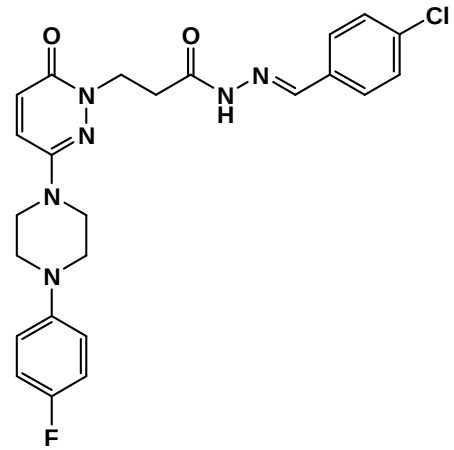

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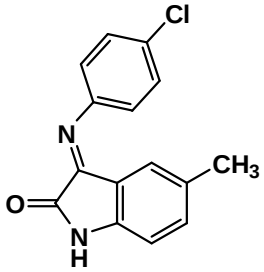
Ozcelik *et al.*, synthesized a series of substituted/nonsubstituted benzalhydrazone derivatives of 3-(6-substituted-3(2H)-pyridazinon-2-yl)propionohydrazide derivatives and evaluated them against AChE. (4-Chlorophenylbenzal)hydrazone derivatives of 3-(6-

(4-fluorophenyl)-3(2H)-pyridazinon-2-yl)propionohydrazide **6** showed an excellent activity against AChE with 98.63 ±1.07% and 99.76 ±1.54% inhibition at 0.1 mM and 0.2 mM concentrations [Ozcelik *et al.* 2010].

2.1.2.1.4. Anticonvulsant activity

Hydrazones of isatin were evaluated for neurotoxicity and anticonvulsant activity by MES and scPTZ at different dose levels [Sridhar *et al.* 2002]. Eight compounds of the series showed significant anticonvulsant activity at 30 mg/kg dose level. 3-(4-chloro-phenylimino)-5-methyl-1,3-dihydro-indol-2-one **7** showed to be the most potent compound of the series with 87% protection at 100 mg/kg and an ED_{50} of 53.61 mg/kg (scPTZ).

A series of hydrazones of (2-oxobenzoxazoline-3-yl)acetohydrazide **8** were synthesized and their antiepileptic activity was tested in scPTZ test. The 4-fluoro derivative was found to be more active than the others [Cakir *et al.* 2001].



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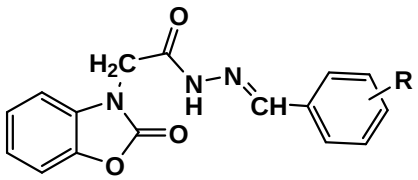

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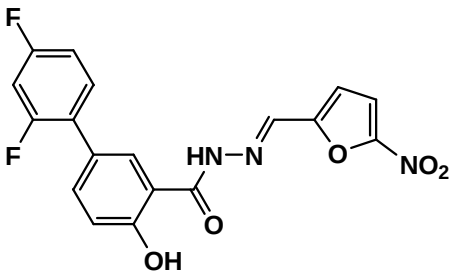
2.1.2.2. **Miscellaneous activities**

2.1.2.2.1. Antimicrobial activity

Kucukguzel *et al*. synthesized diflunisal hydrazide-hydrazone derivatives. 2′,4′-Difluoro-4-hydroxybiphenyl-3-carboxylic acid [(5-nitro-2-furyl)methylene] hydrazide (**9**) showed activity against *S. epidermis* HE-5 and *S. aureus* HE-9 at 18.75 μg/mL and 37.5 μg/mL, respectively. 2′,4′-Difluoro-4-hydroxybiphenyl-3-carboxylic acid [(2,4,6-trimethylphenyl)methylene] hydrazide (**10**) was found to exhibit activity against *Acinetobacter calcoaceticus* IO-16 at a concentration of 37.5 μg/mL, whereas Cefepime, the drug used as standard, was found to be less active against the same microorganisms [Kucukguzel *et al.* 2003].



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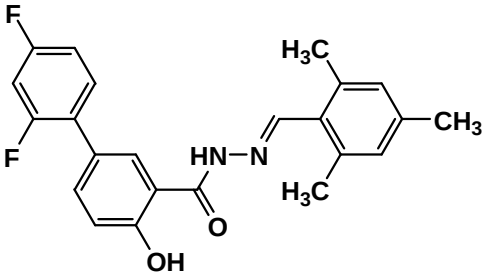

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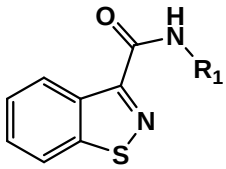
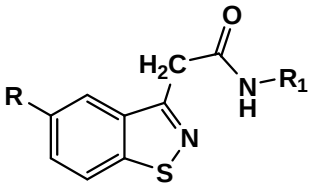


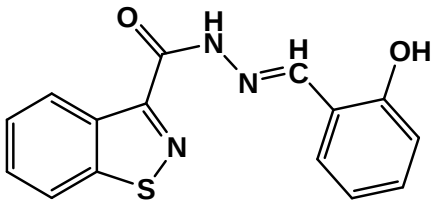


11 (R = H), **12 (**R = CH_3) **13** **14** (R = H), **15** (R = CH_3)

A series of hydrazones derived from 1,2-benzisothiazole hydrazides (R_1=H**) 11-15** as well as the parent cyclic (**11** and **12**) and acyclic (**13, 14** and **15**) 1,2-benzisothiazole hydrazides, were synthesized and evaluated as antibacterial and antifungal agents. All of the 2-amino-1,2-benzisothiazole-3(2H)-one derivatives, belonging to series **11** and **12** showed good antibacterial activity against Gram positive bacteria. Most of them were also found to be active against yeasts [Vicini *et al.* 2002].

2.1.2.6. Antitumor Activity

Several benzo[*d*]isothiazole hydrazones have been synthesized and tested for antitumoral activity. Compound **16,** bearing a hydroxy group at *o*-position of the benzylidene moiety, was the most potent, with the IC_{50} against the various cell lines ranging between 0.5 and 8.0 μM, thus acting equally potent as 6-mercaptopurine against the haematological tumors [Vicini *et al.* 2006].



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2.2. REVIEW ON SEMICARBAZONES

Semicarbazones bearing R-NH-(CO)-NH-N=C-R^1R^2 moiety have been well documented as novel scaffolds for the development of new therapeutic agents for the treatment of CNS related disorders [Pandeya *et al.* 2002; Raja *et al.* 2007; Siddiqui *et al.* 2007].

2.2.1. Chemical review on semicarbazones

Semicarbazones are usually obtained by the condensation reaction between the semicarbazide and suitable aldehydes or ketones (**Figure 2.3.**).

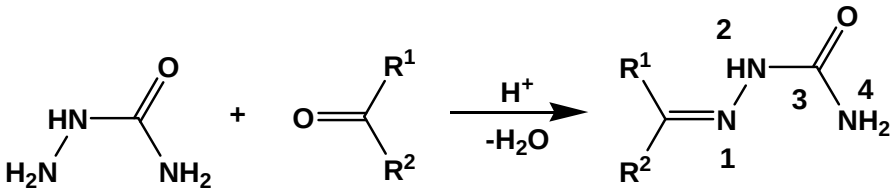


Figure 2.3. Synthesis and numbering scheme of semicarbazones

According to IUPAC recommendations, semicarbazones are named by adding the class name 'semicarbazone' after the name of condensing aldehydes or ketone. The IUPAC numbering scheme for semicarbazones is as shown in **Figure 2.3.**

Semicarbazones predominantly exist in the amido form in the solid state. However, due to the interaction of the solvent molecules, they can exhibit an amido-iminol (keto-enol type) tautomerism (**Figure 2.4.**) in the solution state. Amido form acts as a neutral (bidentate) ligand and the iminol form can deprotonate and serve as anionic (or monoanionic bidentate) ligand in metal complexes, thereby indicating that semicarbazones are versatile ligands in both neutral and anionic forms.

Semicarbazone moiety has an efficient electron delocalization with both the tautomeric forms and hence the delocalization of electron charge density enhance with the aromatic substitution on the semicarbazone skeleton. These classes of compounds also behave as chelating ligands when reacted with metallic cations resulting in the formation of metal complexes. Upon coordination to a metallic (metal) center, the delocalization of electrons is further increased through the metal chelation (metal chelate rings). The coordination possibilities are further increased if the substituent has additional donor atoms.

The backbone skeleton of the free unsubstituted semicarbazones in the solid state are usually planar with O atom trans to the azomethine N atom. However, few exceptions to this rule of semicarbazones do exist [Casas *et al.* 2000]. Even though there are several electronic and steric factors contributing to the adoption of this rearrangement, the most

important is probably that the trans arrangement places the amine and azomethine nitrogen atoms in relative positions as shown in **Figure 2.5.** suitable for the formation of intramolecular hydrogen bonding [Brown and Agarwal 1978].

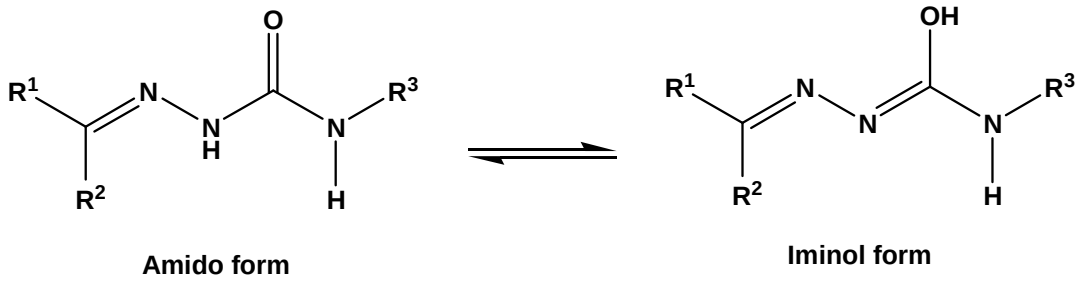


Figure 2.4. Amido-iminol tautomerism of semicarbazone

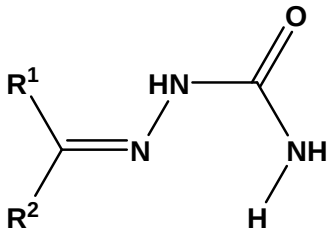


Figure 2.5. Geometry of O atom trans to the azomethine N atom

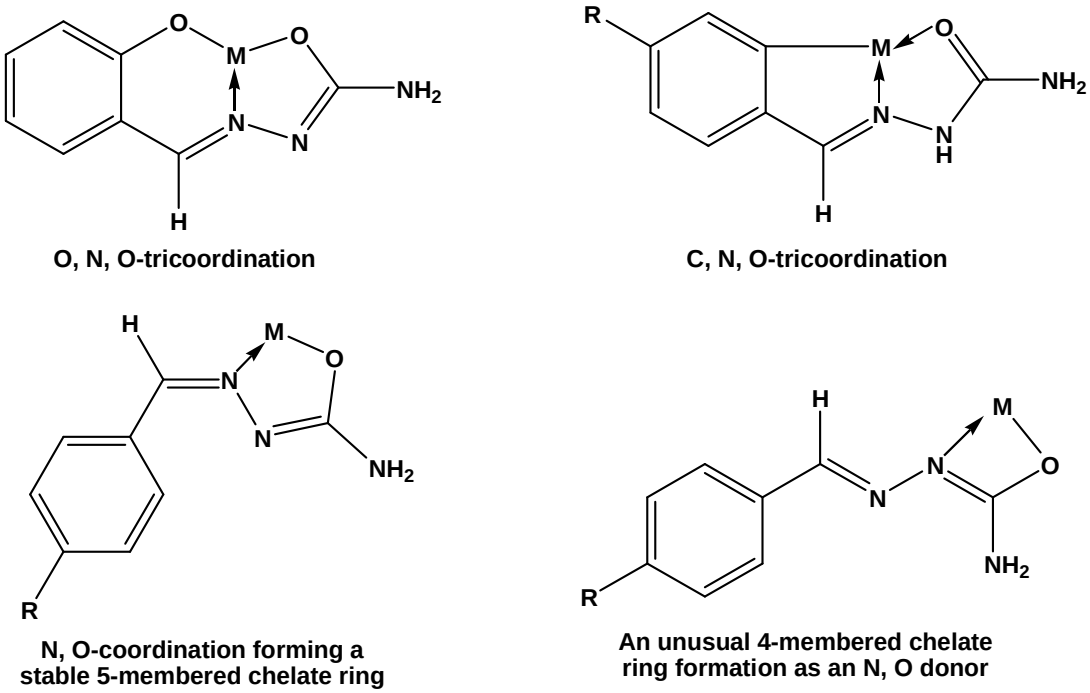


Figure 2.6. Different coordination modes of semicarbazones with transition metals

The semicarbazones demonstrate a diversity of coordination modes with transition metals (**Figure 2.6.**). The coordination mode is influenced by the number and type of substituents. This is because the active donor sites of the ligand vary depending upon the type of substituents. It has been reported that the coordination mode of the semicarbazone is very sensitive towards minor variations in the experimental conditions, the nature of the substituents on the carbonyl compound and the metal salt [Basuli *et al.* 2001].

2.2.1.1. General route for the synthesis of semicarbazones

The general procedure for the synthesis of semicarbazone analogues is as illustrated in **Figure 2.7.** Aryl amine is treated with sodium cyanate in the presence of glacial acetic acid which results in the formation of corresponding aryl urea which on further reaction with hydrazine hydrate yields corresponding semicarbazide (hydrazide carboxamide). Semicarbazide on further reaction with appropriate aldehydes or ketones results in the formation of corresponding semicarbazones [Siddiqui et al. 2007].

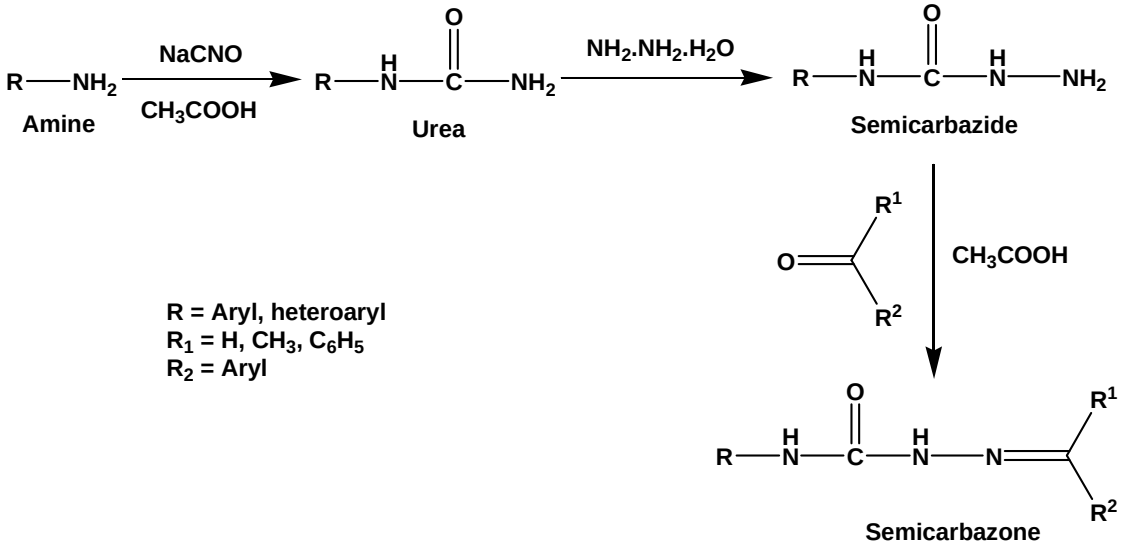


Figure 2.7. General scheme for the synthesis of semicarbazones

2.2.2. Biological review on semicarbazones

Semicarbazones present a wide range of biological activities such as antibacterial, antifungal, antihypertensive, hypolipidemic, antineoplastic, hypnotic, anticonvulsant, etc (**Figure 2.8.**). The biological properties of semicarbazones are often related to metal ion coordination, due to the ability to form terdentate chelates (**Figure 2.6.)** with transition metal ions bonding through oxygen and/or azomethine nitrogen atoms [Pandeya and

Dimmock 1993]. Lipophilicity, which controls permeation across the cell, can be modified by coordination and the metal complex can be more active than the free ligand. The mechanism of action can involve binding to a metal *in vivo* or the metal complex may be a vehicle for activation of the ligand as the cytotoxic agent. Moreover, coordination may lead to significant reduction of drug-resistance [West *et al.* 1991].

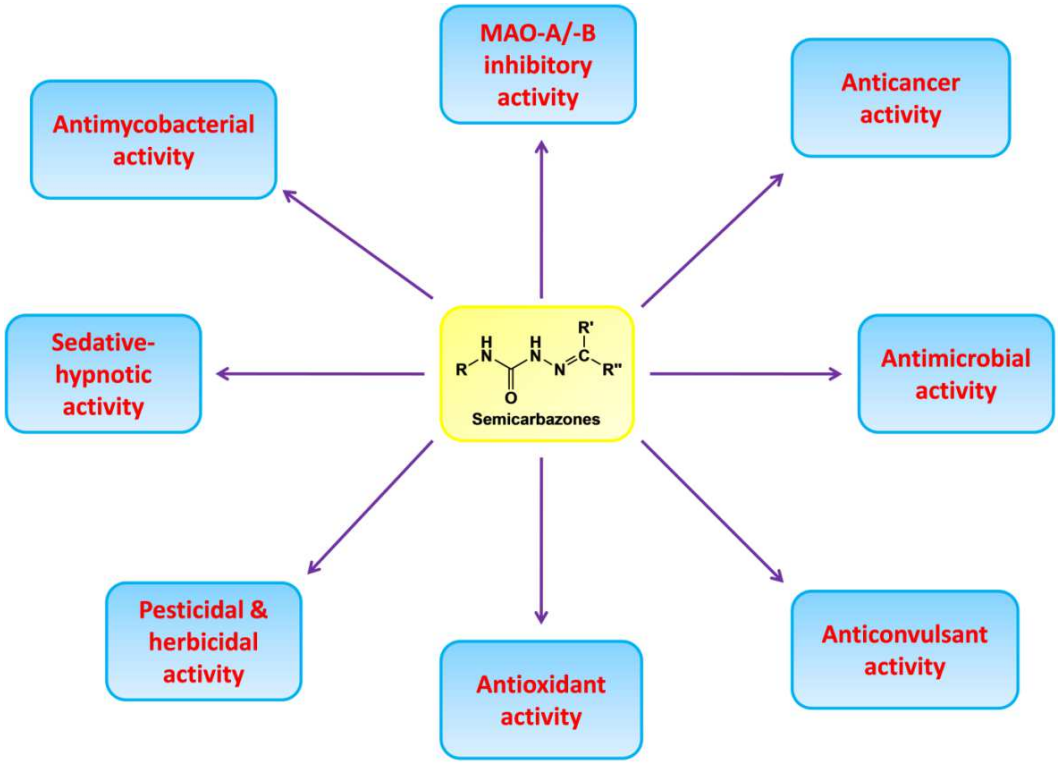


Figure 2.8. Various biological actions of semicarbazones

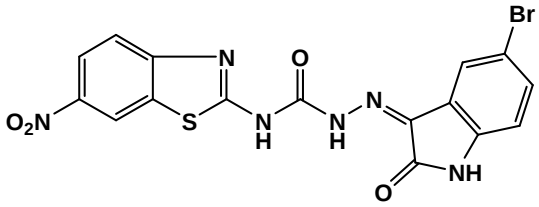
In addition to these, many other activities of semicarbazones have been reported, such as their antimicrobial [Singh *et al.* 1996], pesticide [Anderson *et al.* 2000], herbicide [Copping *et al.* 1983], and hypnotic [Pandeya *et al.* 1999] properties. Moreover, semicarbazones are widely used as spectrophotometric agents for the analysis of metal ions [Atalay and Akgemci 1998].

2.2.2.1. CNS activities

2.2.2.1.1. MAO inhibitory activity

Tripathi *et al.* synthesized a chemical library of 6-nitrobenzothiazole derived semicarbazones and evaluated them for the MAO-B inhibitory activity. 1-[(4-Chlorophenyl)-(phenyl)methylene]-4-(6-nitrobenzothiazol-2-yl)semicarbazide **17**

emerged as the lead MAO-B inhibitor, with top ranking in both the experimental MAO-B assay (IC_{50} = 0.004 µM) and in computational docking studies (K_i = 1.08 µM) [Tripathi *et al.* 2013].



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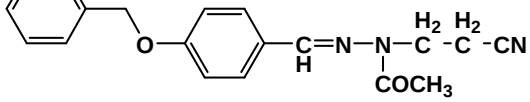

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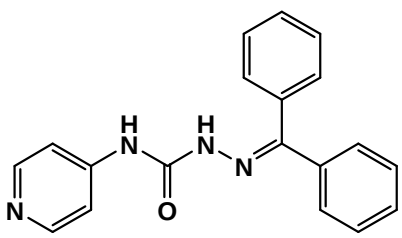
Bernard *et al*. described the synthesis of 21 new substituted acyl hydrazones of various aromatic aldehydes and 4-(benzyloxy)acetophenone, and four substituted semicarbazones of benzaldehyde and 4-(benzyloxy)benzaldehyde and evaluated them for the monoamine oxidase A and B inhibitory activities. The 4-(benzyloxy) phenyl group contributing to a high lipophilicity led to the most active compounds and the most active compound **18** was found to exhibit an IC_{50} value of 3.0 nM (MAO-A/MAO-B selectivity = 33000). It was found to act as a reversible and probably tight binding inhibitor. Some of the new inhibitors might find use in the symptomatic treatment of neurological diseases [Bernard *et al.* 1995].

2.2.2.1.2. AChE inhibitory activity

Sinha *et al.*, synthesized some new semicarbazones of 4-aminopyridine and evaluated them for antiamnesic, cognition enhancing and anticholinesterase activities. The results presented a significant cognition enhancing effect on elevated plus maze model with a significant reversal of scopolamine-induced amnesia in addition to a significant inhibition in acetylcholinesterase (AChE) activity in specific brain regions. Compound **19** (IC_{50} = 0.052 ± 0.01 µM) exhibited significant antiamnesic and cognition enhancing activity which was comparable with standard drug donepezil [Sinha *et al.* 2013].



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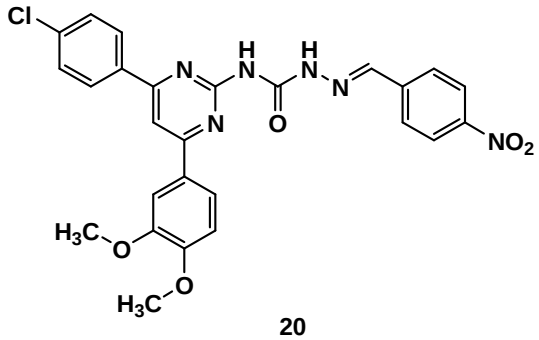
2.2.2.1.3. Anticonvulsant activity

Ozair *et al*., synthesized a series of *N*-(4,6-substituted diphenylpyrimidin-2-yl) semicarbazones and tested for their anticonvulsant activity against MES and scPTZ screening tests. Most of the compounds displayed good anticonvulsant activity with lesser neurotoxicity. The most active compound of the series N^1-[4-(4-chlorophenyl)-6-(3,4-dimethoxyphenyl)-pyrimidin-2-yl]-N^4-(4-nitrobenzaldehyde-)semicarbazone **20** was devoid of any neurotoxicity [Alam *et al.* 2010].



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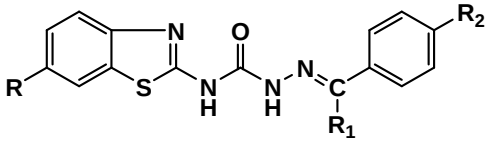

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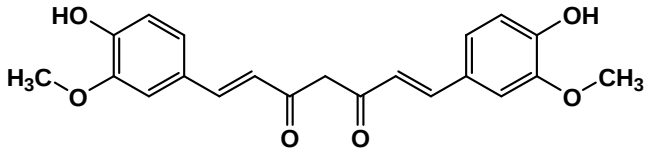
A series of 1-(4-substituted phenyl) ethan-1-one-N-(6-substituted-1,3-benzothiazol-2-yl) semicarbazones **21** were synthesized and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies. Majority of the compounds were active in MES screen [Siddiqui *et al.* 2007].

2.2.2.2. Miscellaneous activities

2.2.2.2.1. Antitumour activity

Dutta *et al.* synthesized a new semicarbazone derivative of curcumin (CRSC) and it for its antioxidant, antiproliferative, and antiradical activity and compared with those of curcumin (CR) **22a**. The antioxidant activity was tested by their ability to inhibit radiation induced lipid peroxidation in rat liver microsomes. The antiproliferative activity was tested by studying the *in vitro* activity of CRSC **22b** against estrogen dependent breast cancer cell lines MCF-7. Kinetics of reaction of (2,2′-diphenyl-1-picrylhydrazide) DPPH, a stable hydrogen abstracting free radical was studied to measure the antiradical activity. The results suggested that the probable site of attack for CRSC indicated efficient antioxidant and antiproliferative activity although its antiradical activity was less than that of CR [Dutta *et al.* 2005].



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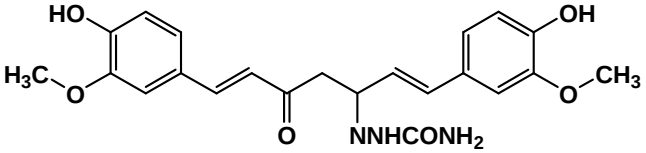
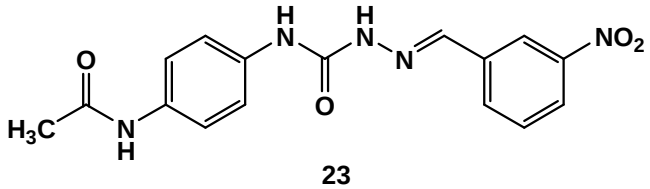


22b

2.2.2.2.2. Antimicrobial activity

Sriram *et al.* while working on the synthesis and screening of antitubercular agents, identified N^1-(4-acetamido phenyl)-N^4-(2-nitrobenzylidene)semicarbazone **23**, which inhibited *in vitro M. tuberculosis* H37 Rv; 100% inhibition at 1.56 µ/mL [Sriram *et al.* 2004].



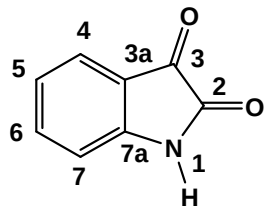
23

Thus, due to their good biological activities, complexing properties and analytical application; semicarbazones and their Schiff bases has been the subject of many studies and still needed to be explored for the future development of new drugs against various targets.

2.3. REVIEW ON ISATIN

Isatin **24** (1H-indole-2,3-dione) is a synthetically versatile moiety and a valuable template in the field of pharmaceutical chemistry [Shvekhgeimer 1996]. It is used for the synthesis of an array of heterocyclic compounds and drugs.

Isatin was first obtained by Erdmann [Erdmann 1840] and Laurent [Laurent 1840] in 1841 as a product from the oxidation of indigo dye by nitric acid and chromic acids. The various positions on the isatin ring are numbered in the manner indicated, as shown in **Figure 2.9.**



24

Figure 2.9. Structure of isatin

2.3.1. Occurrence of isatin

Isatin is one of the constituents of plants of the genus Isatis [Guo and Chen, 1986], in Calanthe discolour LINDL. [Yoshikawa *et al.* 1998] and in *Couroupita guianensis* Aubl. [Bergman *et al.* 1985]. It is also found to be a part (constituent/component) of the secretion from the parotid gland of *Bufo* frogs [Wei *et al.* 1982], and in humans as a metabolic derivative of adrenaline [Ischia *et al.* 1988; Palumbo *et al.* 1989; Halket *et al.* 1991]. Various substituted isatins are also found in plants, viz. melosatin alkaloids (methoxy phenylpentyl isatins) isolated from the Caribbean tumorigenic plant *Melochia tomentosa* [Kapadia *et al.* 1977; Kapadia *et al.* 1980; Kapadia and Shukla 1993], 6-(3'-methylbuten-2'-yl)isatin was obtained from the fungus *Streptomyces albus* [Grafe and Radics 1986; Graefe *et al.* 1986] and 5-(3'-methylbuten-2'-yl)isatin from *Chaetomium globosum* [Breinholt *et al.* 1996].

Isatin is a precursor in the syntheses of a wide range of drugs like pirquinozol, talnetant, tacrine, dibucaine, ciclazindol, methisazone, oxyphenisatin, etc. Moreover, a variety of tryptamine derivatives, including many substituted with alkyl or aryl groups in the α-position have been synthesized from various intermediates of isatin. For example, 6-chloroisatin is used as a precursor in the synthesis of Ziprasidone, likewise, 7-trifluoromethyl isatin in the synthesis of mefloquine, N-phenylisatin for linopirdine, N-dichlorophenyl isatin for diclofenac, etc.

2.3.2. Chemical review on isatin and its derivatives

2.3.2.1. Synthesis of isatin and its derivatives

The classical methods for the synthesis of isatins are Sandmeyer's method and the Stolle procedure, both of which use aniline as a starting material (**Figure 2.10.**).

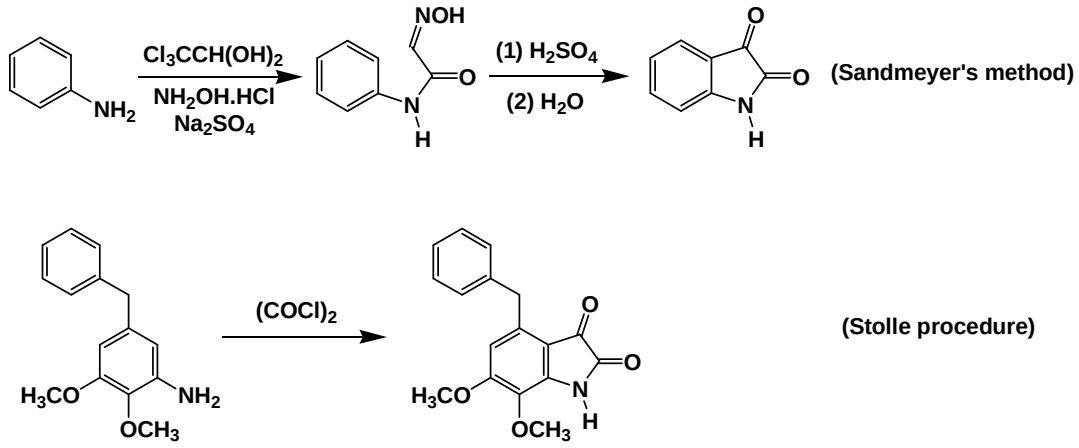


Figure 2.10. Synthesis of isatin and its derivatives

2.3.3. Biological review on isatin and its derivatives

Isatin possesses a wide range of biological activities (**Figure 2.11.**). Isatin have been found in mammalian tissue and their function as a modulator of biochemical processes has been the subject of several discussions. In addition to its effect on central nervous system, its physiological effects protect against stress and certain infections.

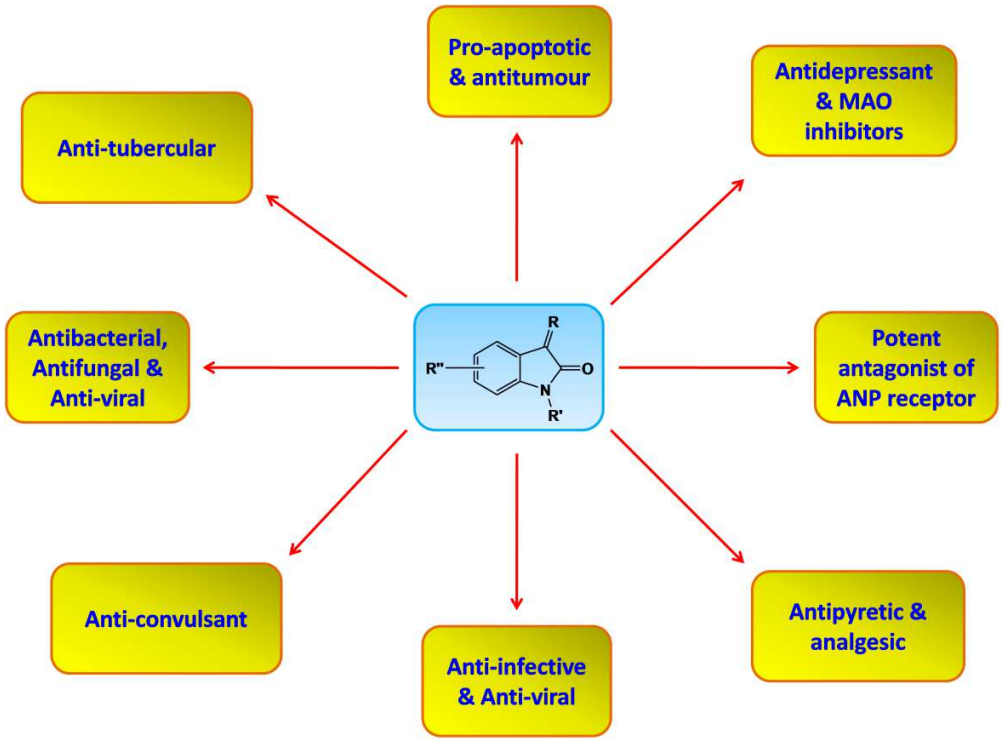


Figure 2.11. Various biological actions of isatin derivatives

In 1988, isatin was identified as a major constituent of tribulin, a low-molecular-weight inhibitor of MAO-B [Glover *et al.* 1988]. Moreover, it has been reported that urinary

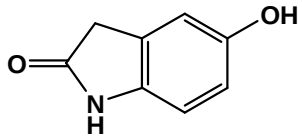
concentrations of isatin tend to increase in patients with Parkinson's disease depending upon the severity of disease suggesting that urinary isatin may turn out to be a diagnostic marker for the clinical severity of Parkinson's disease and that endogenous isatin, a new biological modulator, may play a role in the regulation of brain levels of ACh by increasing the level of DA under stress, isatin in the urine and brain [Hamaue *et al.* 1992; Hamaue *et al.* 1994] of stroke-prone spontaneously hypertensive rats. Further, Kumar *et al*. [Kumar *et al.* 1993] reported that isatin inhibits acetylcholinesterase (AChE) activity in rat brain and erythrocytes. Additionally, isatin has been shown to inhibit many enzymes in various tissues, such as acid phosphatase [Singh *et al.* 1977], alkaline phosphatase, and xanthine oxidase, hyaluronidase [Kumar *et al.* 1977] as well as MAO [Medvedev *et al.* 1996]. It has also been found to act as an antiseizure agent [Chocholova and Kolinova 1979].

Some of the recent developments of isatin based medicinal chemistry are described below:

2.3.3.1. CNS activities

2.3.3.1.1. MAO inhibitory activity

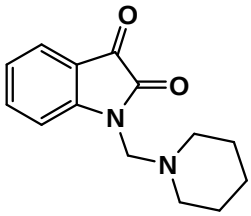
Arias *et al.*, compared the *in vitro* inhibition of MAO-A and MAO-B on rat brain non-synaptic mitochondria using 5-hydroxyoxindole with isatin derivatives. 5-Hydroxyoxindole **25** was found to be less potent MAO-A inhibitor (IC_{50} = 56.8 μM) than isatin (IC_{50} = 31.8 μM) and especially 5-hydroxyisatin (IC_{50} = 6.5 μM), but it was highly selective MAO-B inhibitor (IC_{50} MAO-A:IC_{50} MAO-B = 0.044) [Arias *et al.* 2004].



25

2.3.3.1.2. AChE inhibitory activity

Ozgun *et al.*, synthesized Mannich bases of isatin and evaluated them for AChE inhibitory activities. The isatin Mannich bases incorporating (1-[piperidin-1-yl (**26**)/morpholin-4-yl (**27**)/Nmethylpiperazin-1-yl (**28**)]methyl)-1H-indole-2,3-dione) moieties demonstrated impressive inhibition profiles at nanomolar level (IC_{50} = 1.66, 1.86 and 2.34 nM respectively for **26**, **27** and **28**) against AChE [Ozgun *et al.* 2016].



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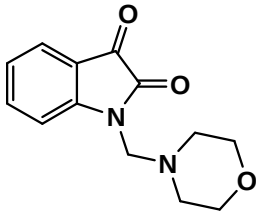

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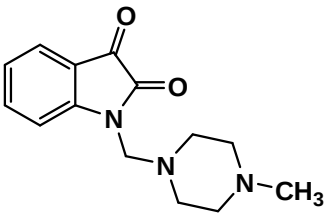

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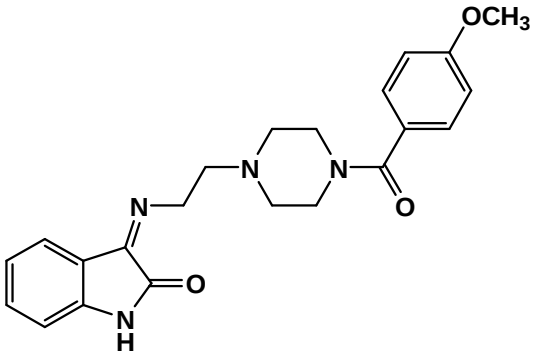
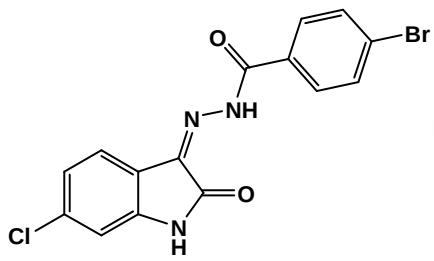


29

Rahmani-Khajouei *et al.*, synthesized a new series of donepezil-like derivatives with isatin substructure and assessed their anti-AChE activity *in vitro*. Most of the tested compounds demonstrated superior activity than donepezil. Among them, 3-(2-(4-(4-methoxybenzoyl)piperazin-1-yl)ethylimino)indolin-2-one **29** was found to be most active compound with an IC_{50} value of 0.01 nM against AChE [Rahmani-Khajouei *et al.* 2015].

2.3.3.1.3. Anticonvulsant activity

Pandeya *et al.* synthesized a series of isatin-3-hydrazone, a series of substituted isatin semicarbazones and related bioisosteric hydrazones to meet the structural requirements essential to exhibit anticonvulsant properties. Compound 6-chloroisatin-3- (4-bromophenyl)-semicarbazone **30** emerged as the most active analogue of the series showing good activity in all the three tests MES, scPTZ and scSTY and was found to be more active than phenytoin and valproic acid [Pandeya and Raja 2002].



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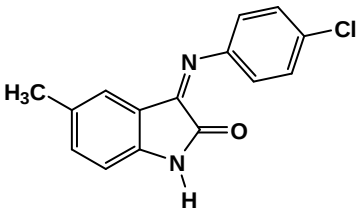

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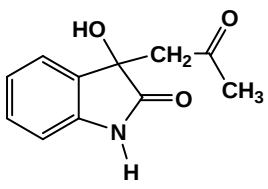


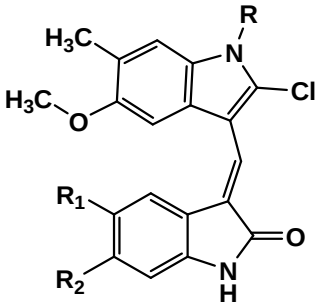
32

Sridhar *et al.* reported the synthesis of 3-(4-chlorophenylimino)-5-methyl-1,3-dihydro-indole-2-one. Compound **31** was found to be most active compound showing 87% protection at the dose of 100 mg/kg with an ED_{50} value of 53.61 mg/kg [Sridhar *et al.*, 2002].

Popp *et al*. studied comparative anticonvulsant activity of different isatin derivatives. They found that 3-hydroxy-3-acetonyloxindole **32** which was obtained from the condensation of isatin and acetone, exhibited greater anticonvulsant activity than 3-hydroxyl-3-phenacyloxindole [Popp and Donigan 1979].

2.3.3.2. Miscellaneous activities

2.3.3.2.1. Antioxidant activity



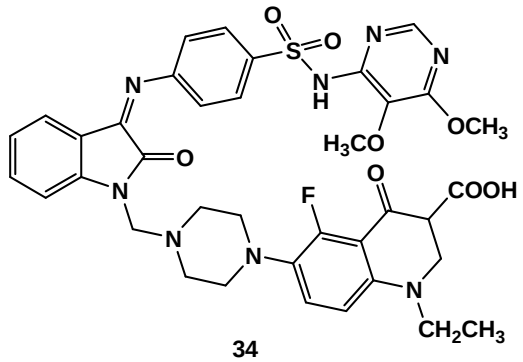
33a-c

33a (R = CH_3, R_1 = OH, R_2 = CH_3)
33b (R = CH_3, R_1 = OH, R_2 = H)
33c (R = 1-chloro-4-ethylbenzene, R_1 = OH, R_2 = CH_3)

Burnelli *et al*. reported the synthesis of 3,3-bis (4-amino-2,5-dimethoxyphenyl)-1,3-dihydroindol-3one derivatives **33** [Andreani *et al.* 2010]. The synthesized compounds were evaluated against Trolox equivalent antioxidant activity (TEAC) assay at pH=7.4 and compounds possessing phenolic OH or OCH_3 groups in their structure **33a-c** showed good chemical antioxidant activity.

2.3.3.2.2. Antibacterial activity

Pandeya *et al.* reported the synthesis of Mannich bases of norfloxacin with formaldehyde and several isatin derivatives [Pandeya *et al.* 2000]. The synthesized compounds were evaluated for their *in vitro* antibacterial activity against many pathogenic bacterial strains (*S. typhimurium, V. parahaemolyticus, V. Cholera,* etc.). Compound **34** (4.8 times) was found to be more active (0.018-0.61 μg/ml) than that of norfloxacin (1.22 μg/ml) against *B. subtilis*.



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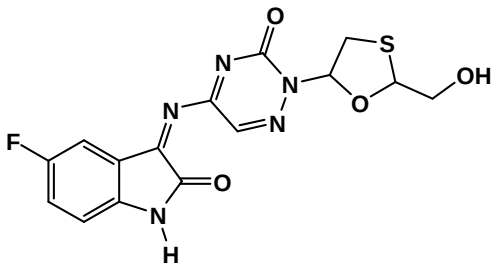


35

2.3.3.2.3. Cytotoxic activity

Solomon *et al.* reported the synthesis of isatin-benzothiazole analogs [Solomon *et al.* 2009]. Among the synthesized compound 4-bromo-1-diethylaminomethyl-1H-indol-2,3-dion 34 emerged as most active compounds. The cytotoxic effect of **35** was 10-15 folds higher on cancer than non-cancer cells.

From the above discussion, it has been observed so far, that the alterations on isatin moiety displayed valuable biological activities and these alterations can be utilized to develop potentially active agents in future investigations. Thus, the search to explore many more modifications on isatin moiety needs to be continued.

2.4. REVIEW ON THIAZOLES

Many compounds bearing five-membered heterocyclic rings in their structure have an extensive spectrum of biological activities. The search for new biologically active thiazole analogues continues to be an area of intensive investigation in medicinal chemistry.

2.4.1. Chemical review on thiazoles

Thiazole, or 1,3-thiazole **36** belongs to a class of organic compounds called azoles. Thiazole is aromatic, heterocyclic organic compound containing both sulfur and nitrogen; that has a five-membered molecular ring structure, C_3H_3NS. Thiazole can also be considered as a functional group. The term 'thiazole' also refers to a large family of derivatives.

The various positions on the thiazole ring are numbered in the manner indicated, with the sulfur having priority over other family members as shown in **Figure 2.12.** The calculated pi-electron density marks C5 as the primary site for electrophilic substitution, and C2 as the site for nucleophilic substitution (**Figure 2.12.**).

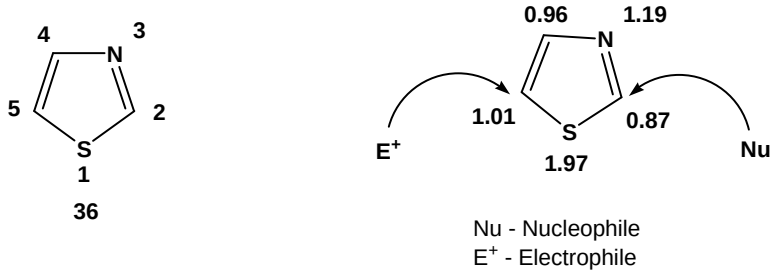


Figure 2.12. Structure and active centers of thiazole

Thiazole rings are planar and aromatic on the basis of delocalization of a lone pair of electrons from the sulfur atom completing the needed 6 π electrons to satisfy Huckel's rule (**Figure 2.13.**).

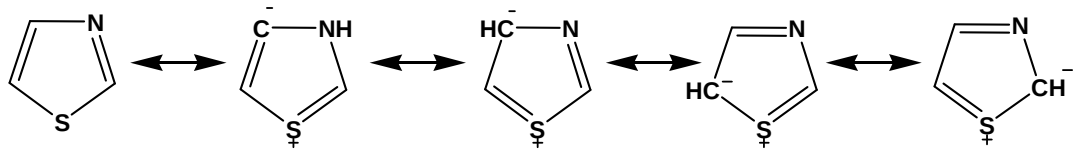


Figure 2.13. Resonance in thiazole

2.4.2. Occurrence of thiazoles and thiazolium salts

Thiazoles are found in a range of specialized products, often fused with benzene derivatives, the so-called benzothiazoles (**BTA**), found in luciferin, the chemical found in firefly. Besides, the thiazole moiety is a crucial part of vitamin B_1 (thiamine) and epothilone. Thiazoles are present in biomolecules as well.

Many thiazoles are flavoured compounds. A number of thiazole *viz.* 2-methylthiazole, 4-methylthiazole, 5-methylthiazole and 5-butlythiazole are all found in roasted peanuts. They are found in foods thiazole contributes to the flavor of brewed coffee. Cooked beef aroma also contains many thiazoles.

Thiazoles have been used to give N-S free carbenes and transition metal carbene complexes. The amino atom can be alkylated to create a thiazolium cation; thiazolium salts acts as catalysts in the Stetter reaction and the Benzoin condensation.

The substituted thiazoles exhibit a number of characteristic pharmacological features such as relative stability and ease of starting material, enhanced lipid solubility with hydrophilicity and easy metabolism of compounds.

2.4.3. Biological review on thiazoles and its derivatives

Thiazoles are important class of heterocyclic compounds, found in many potent biologically active molecules such as sulfathiazol (antimicrobial drug), ritonavir

(antiretroviral drug), abafungin (antifungal drug) and bleomycine and tiazofurin (antineoplastic drug) [Siddiqui *et al.* 2009]. In recent times, the applications of thiazoles were found in drug development for the treatment of allergies [Hargrave *et al.* 1983], hypertension [Patt *et al.* 1992], inflammation [Sharma *et al.* 2009], schizophrenia [Jean *et al.* 1990], bacterial [Tsuji and Ishikawa 1994], HIV infections [Bell *et al.* 1995], hypnotics [Ergenc *et al.* 1999] and more recently for the treatment of pain [Carter *et al.* 1999], as fibrinogen receptor antagonists with antithrombotic activity [Badorc *et al.* 1997] and as new inhibitors of bacterial DNA gyrase B [Rudolph *et al.* 2001]. Moreover, a very well-known non-steroidal anti-inflammatory drug meloxicam is also a thiazole derivative.

Thus, thiazole derivatives are known to exhibit a wide range of biological activities such as antibacterial, antifungal, antiinflammatory, antitubercular, anti-HIV, neuroprotective and antioxidant, anticonvulsant, anticancer, antidiabetic and antihypertensive (**Figure 2.14.**).

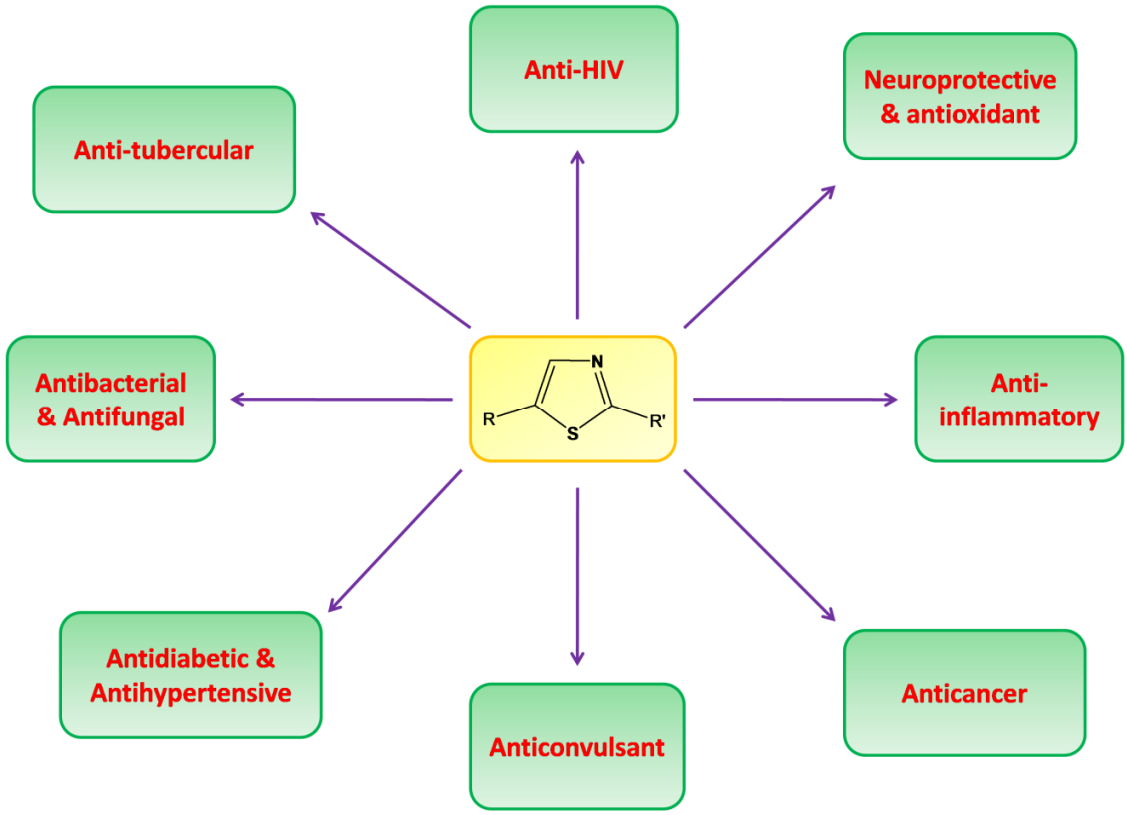


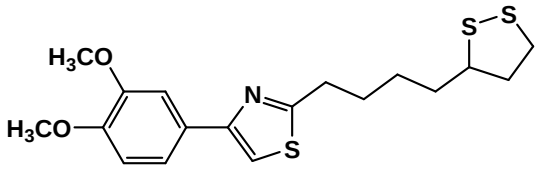
Figure 2.14. Various applications of thiazoles

Thiazoles containing N=C-S moiety has been employed as antipsychotic and anti-bacterial. Thiazoles derivatives particularly amino thiazoles play vital role in pharmaceutical practices.

2.4.3.1. CNS activities

2.4.3.1.1. Neuroprotective activity

Koufaki *et al.*, synthesized 1,2-dithiolane derivatives and screened for neuroprotective activity. Compound **37** was found to be highly neuroprotective [Koufaki *et al.* 2007].



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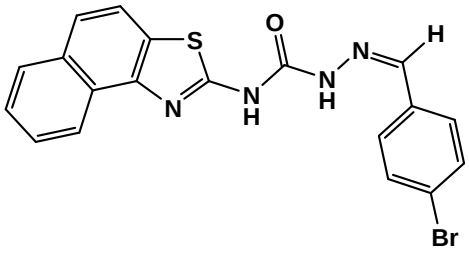


38

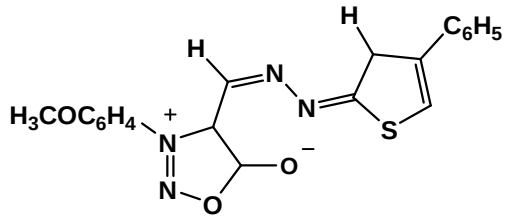
2.4.3.1.2. Anticonvulsant activity

Azam *et al.* synthesized a series of N4-(naphtha[1,2-d]thiazol-2-yl)semicarbazides and evaluated for their anticonvulsant and neurotoxicity studies. Compound **38** was found to be most active [Azam *et al.* 2009].

2.4.3.2. Miscellaneous activities

2.4.3.2.1. Antioxidant activity

Shih *et al.*, synthesized a series of sydnonyl substituted thiazolidinone and thiazoline derivatives and evaluated them for antioxidant activity. Compound **39** exhibited significant DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity, comparable to that of vitamin E [Shih and Ying 2004].



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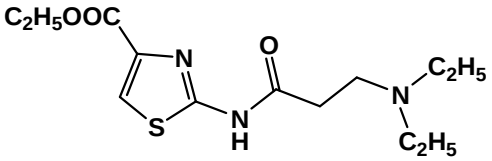


40

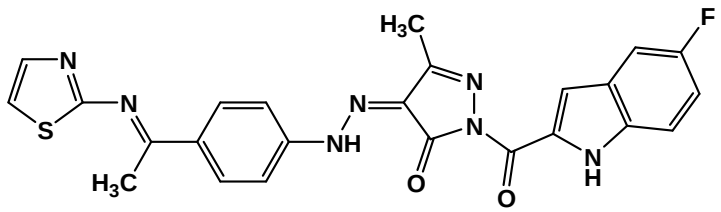
2.4.3.2.2. Antitumor activity

The synthesis of several new ethyl-2-substituted aminothiazole-4-carboxylate analogs have been described and the prepared compounds were tested for their in vitro antitumor activity against 60 human tumor cell lines by the National Cancer Institute (NCI). Ethyl-

2-[3-(diethylamino)-propanamido]-thiazole-4-carboxylate **40** exhibited remarkable activity against RPMI-8226 leukemia cell line with GI value of 0.08 μM and a broad spectrum activity against all the tumor cell lines with GI (MG-MID) value of 38.3 μM [El-Subbagha *et al.* 1999].

2.4.3.2.3. Antimicrobial activity

3-Methyl-1-[(5-substituted-1H-indol-2-yl)carbonyl]-4-{[4-(substitutedthiazol-2-yl) i-minoethyl)phenyl]hydrazono}-2-pyrazolin-5-one derivatives were synthesized and tested for their antimicrobial activity against six strains of bacteria and three fungal strains. Compound **41** exhibited excellent antifungal activity [Mostafa and Abd El-Salam 2013].



41

Thus, it can be concluded that modifications on the thiazole moiety resulted in a range of biological activities. These modifications can be utilized further to develop and exploit thiazole containing derivatives as potential therapeutic agents. Thus the expedition to investigate and explore additional modifications on the thiazole moiety is requisite.

2.5. REVIEW ON BENZOTHIAZOLE (BTA)

The structure-activity concept has emerged as a prolific approach for the novel drug discovery and is a promptly budding subject in medicinal chemistry. BTAs are the archetypal structures, with their intrinsic affinity for diverse biological receptors. BTA represents an ideal source of core scaffolds and capping fragments for the design and synthesis of targeted molecules, whose exploitation enables the medicinal chemist to rapidly discover biologically active compounds across an array of therapeutic areas. Nitrogen and sulphur containing heterocycles play an important role, not only for life science, but also in many other industrial fields related to special and fine chemistry. Among them, BTAs comprise a class of therapeutic compounds that exert a wide range of biological activities [Horton *et al.* 2003; DeSimone *et al.* 2004; Dolle 1999].

2.5.1. Occurrence of BTA

BTAs rarely occur in various marine or terrestrial natural compounds, which have useful biological activities. They form part of the structure of firefly luciferin and are also known as aroma constituents of tea leaves and cranberries or flavor compounds produced by the fungi *Aspergillus clavatus* and *Polyporus frondosus* [Gunawardana *et al.* 1988; 1989]. BTA derivatives have been continously fascinating researchers because of their varied biological activities viz. anticancer [Huang *et al.* 2006], antimicrobial [Singh *et al.* 2014], anticonvulsant [Siddiqui *et al.* 2007], antiviral [Akhtar *et al.* 2008], antitubercular [Palmer *et al.* 1971], antimalarial [Burger and Sawhey 1968], antihelmintic [Suresh *et al.* 2013], analgesic [Siddiqui *et al.* 2004], anti-inflammtory [Gurupadayya *et al.* 2005], antidiabetic [Pattan *et al.* 2005] and fungicidal activities [Singh and Segal 1988].

Recently, benzothiazole derivatives have been evaluated as potential amyloid-binding diagnostic agents in neurodegenerative disease [Henriksen *et al.* 2007; Mathis *et al.* 2003], selective fatty acid amide hydrolase inhibitors [Wang *et al.* 2009], LTD4 receptor antagonist [Lau *et al.* 1995], orexin receptor antagonist [Bergman *et al.* 2006], and histamine H_2 antagonists [Apelt *et al.* 2005]. They are also useful as appetite depressants [Rana *et al.* 2008], intermediates for dyes [Razus *et al.* 2007], plant protectants [Papenfuh 1987], imaging agents for β-amyloid plaques [Gan *et al.* 2013], and photographic sensitizers [Parton *et al.* 1995].

Being heterocyclic compounds, BTA derivatives find use in various branches of chemical research, for instance, in polymer chemistry [Kokelenberg and Marve 1970; Cao *et al.* 2013], dyes [Gwon *et al.* 2012; Okoh *et al.* 2014], drugs etc. 2-Substituted BTA derivatives constitute a large group of xenobiotics, which are manufactured worldwide for a variety of applications as shown in **Figure 2.15.** [Seo *et al.* 2000]. The simplest member of the family, benzothiazole is a fungicide [Reemtsma *et al.* 1995]. Methabenzthiazuron (MBTU) is used as herbicide in winter corn crops, slimicides in the paper and pulp industry [Meding *et al.* 1993]. 2-Aminobenzothiazole is used manufacturing some disperse azo dye [Peters and Yang 1995]. Riluzole (2-amino-6-trifluoromethoxybenzothiazole) is marketed by Rhone-Poulenc (Rilutek) for treatment of amyotrophic lateral sclerosis [http://www.drugs.com/pro/rilutek.html] and 2-(4-aminophenyl)benzothiazole evidenced antitumor properties [Shi *et al.* 1996; Hutchinson *et al.* 2002]. BTA derivatives catalyze the formation of sulfide linkages between

unsaturated elastomeric polymers in order to obtain a flexible and elastic cross-linked material. 2-Mercaptobenzothiazole (MBT/BTSH) is the main used rubber accelerator in certain specialty products and even in the tire production [Fiehn *et al.* 1994; Reemtsma 2000].

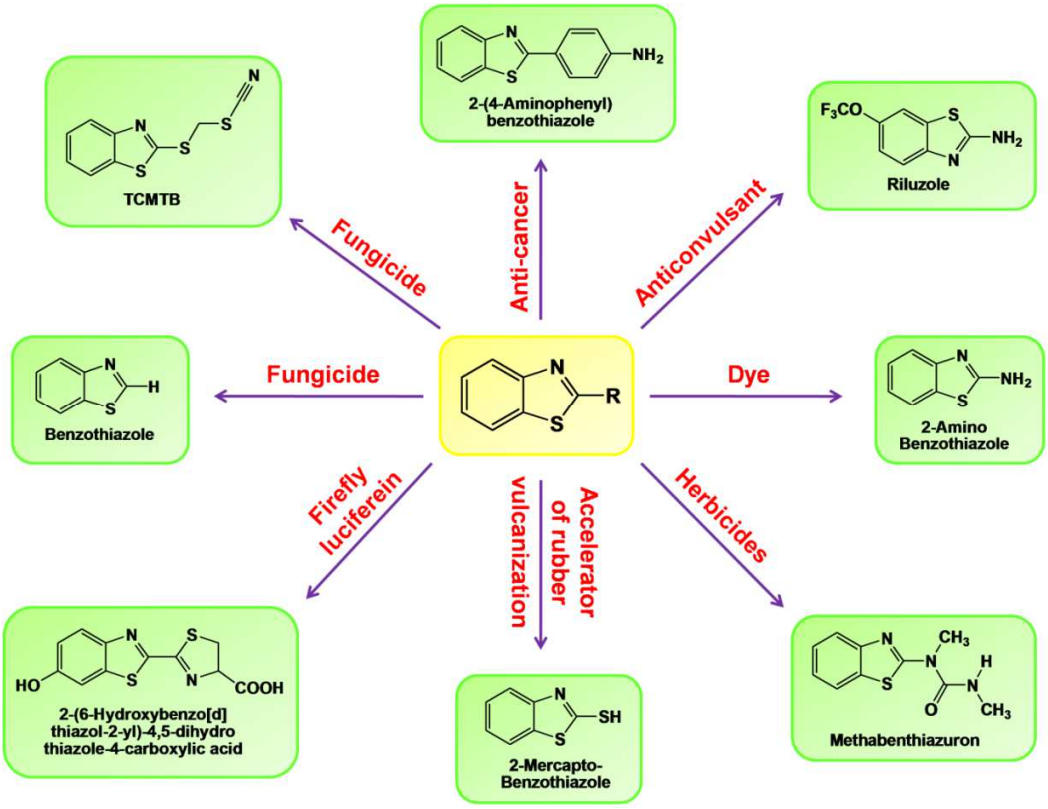
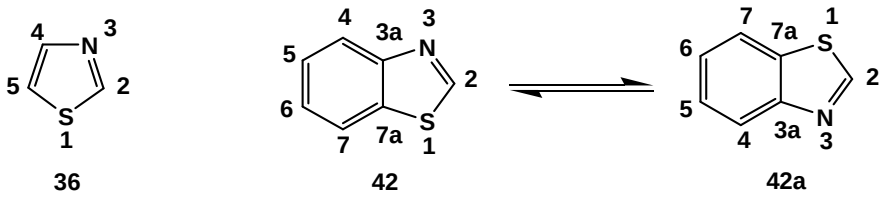


Figure 2.15. Various applications of benzothiazole nucleus

Therefore, the enormous variety of biological effects associated with this scaffold has resulted in the BTA ring system being considered as a privileged structure. The main objectives of BTA syntheses are for the development of more diverse and complex bioactive compounds for biological activity and structure-activity relationship (SAR) studies. Therefore, the synthesis of BTA derivatives has received an increasing attention to synthetic organic chemists and biologists.

2.5.2. Chemical review on benzothiazole

The ring system in which benzene ring is fused to the 4,5-positions of thiazole ring (**36**) is designated as BTA (**42**). It is a completely planar molecule. The various positions on the BTA ring are numbered in the manner indicated, with the sulfur having priority over other family members as shown in **Figure 2.16.**



36 **42** **42a**

Figure 2.16. Tautomerism in benzothiazole

2-substituted BTA was first synthesized by A. W. Hofmann in 1887. Because of diversified activity as well as simple cyclization mechanism, various synthetic routes have been adopted and reported [Fan *et al.* 2011].

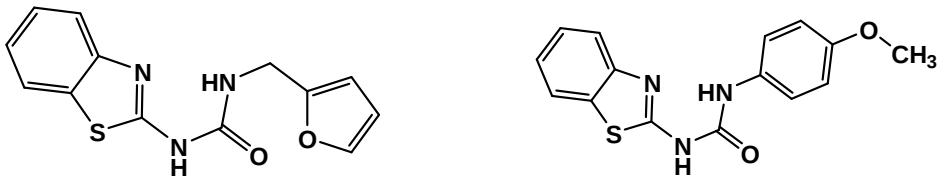
2.5.3. Biological review on BTA and its derivatives

BTA and its analogues are important pharmacophore and honored structures in medicinal chemistry and have featured in a number of clinically used drugs. Several attempts were made for modifying the BTA nucleus to improve their biological activities. Modifications on the BTA nucleus have resulted in a large number of compounds having diverse pharmacological activities. Some of the current developments of BTA based medicinal chemistry is listed below:

2.5.3.1. CNS activities

2.5.3.1.1. Anti-Parkinson activity

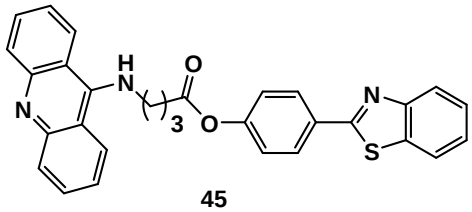
Azam and co-workers synthesized and evaluated BTA-urea derivatives as anti-Parkinsonian agents. Some of the compounds were active in alleviating haloperidol-induced catalepsyin mice. Furfuryl (**43**), 2- and/or 3- methoxy (**44**), substituted phenyl derivatives emerged as potent anti-Parkinsonian agents [Azam *et al.* 2012].



43 **44**

2.5.3.1.2. Anti-AD activity

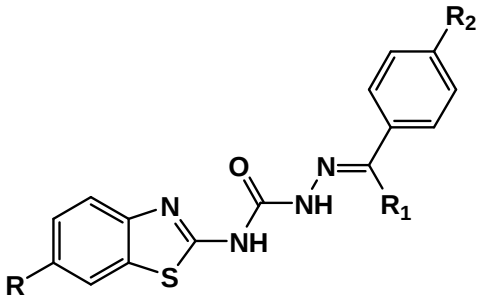
Huang *et al.*, evaluated tacrine-phenylbenzoheterocyclic hybrids as multifunctional anti-AD agents. Compound **45**, tacrine linked with phenyl-BTA by 3-carbon spacers, was found to be most potent AChE inhibitor with an IC_{50} value of 0.017 µM and Aβ aggregation inhibitory activity 52.1% at 20 µM, indicating, this hybrid is an excellent multifunctional drug candidate for AD [Huang *et al.* 2012]



45

2.5.3.1.3. Anticonvulsant activity

BTA containing semicarbazones were synthesized and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies by MES. Compounds **46a-d** displayed 100% protection at 0.5 h. SAR study reveals, substituents like -CH_3, -OCH_3 at the aryl ring with -NO_2 and unsubstituted distant phenyl ring lead to highly potent compounds having longer duration of activity [Siddiqui *et al.* 2007; 2012].



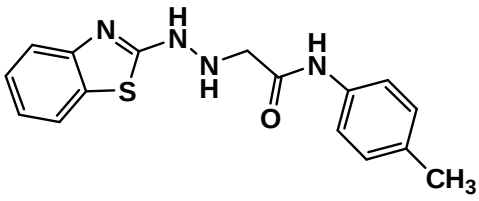
46

46a (R = Cl, R_1 = CH_3, R_2 = H)
46b (R = CH_3, R_1 = CH_3, R_2 = NO_2)
46c (R = OCH_3, R_1 = CH_3, R_2 = NO_2)
46d (R = OCH_3, R1 = C_6H_5, R_2 = H)

2.5.3.2. Miscellaneous activities

2.5.3.2.1. Antioxidant activity

Suresh *et al.*, synthesized 2-hydrazino BTA and screened them for antioxidant activity. All the compounds showed very good antioxidant activity with IC_{50} values in the range 6.8-12.93 µM. Compounds **47** and **48** showed the highest percentage of free radical scavenging activity [Suresh *et al.* 2011].



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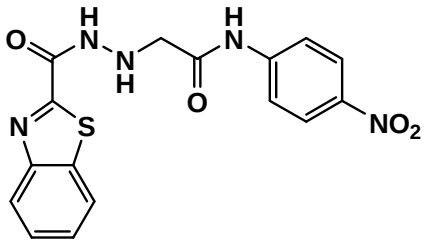
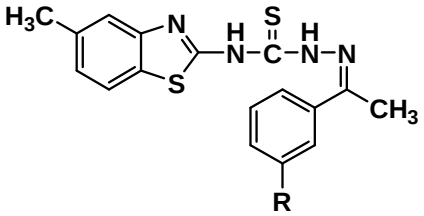


48

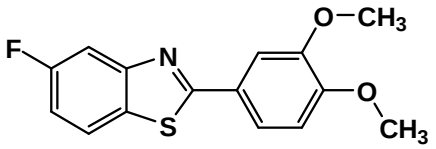
2.5.3.2.2. Antimicrobial activity

2-Substituted BTA derivatives were prepared and tested for antimicrobial activity against both, Gram positive and Gram negative bacteria, with ampicillin as a standard.

Compounds **49a-b** exhibited excellent activities against P. aeruginosa and E. coli, respectively [Pandurangan *et al.* 2010].



49a (R = NO_2), **49b** (R = Br)



50

2.5.3.2.3. Antitumor activity

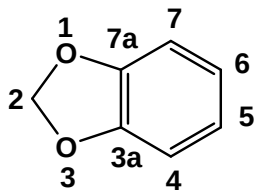
Substituted BTAs such as 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole **50** (PMX 610) have been shown to exhibit exquisitely potent (GI_{50} < 0.1 nM) and selective in vitro antitumor properties in human cancer cell lines (e.g., colon, nonsmaller cell lung and breast subpanels) in addition to remarkable antitumor activity against malignant cell lines [Tan *et al.* 2011; Al-Soud *et al.* 2008].

Apart from the above mentioned activities, BTA derivatives have been also found to exhibit potential applications in other medical fields, such as anti-infective, anti-mosquito agents, anti-mitotic, diuretic, etc.

From the above discussions, it can be clearly stated that the structural BTA ring plays an important role in medicinal chemistry and the related research has been unusually active subjects. Future investigations of this scaffold could give some more encouraging results in the field of medicine. The literature survey would give rise to design of better molecules with enhanced biological properties and higher specificity, and together with development of novel synthetic strategies.

2.6. REVIEW ON 1,3-BENZODIOXOLE

1,3-Benzodioxole or 3,4-(Methylenedioxy)benzene **51** is an oxygen containing heterocyclic compound in which the dioxole ring is fused with the benzene ring. The various positions on the 1,3-Benzodioxole are numbered in the manner indicated, with oxygen having priority over other family members as shown in **Figure 2.17.**



51

Figure 2.17. Structure of 1,3-Benzodioxole

2.6.1. Chemical review on 1,3-benzodioxole and its derivatives

The 1,3-benzodioxole moiety has a great interest by medicinal chemists. It is a ring system in which the methylenedioxy (–O–CH_2–O–), a functional group in organic chemistry, is found attached to an aromatic ring phenyl, where it forms the (methylenedioxy)phenyl or benzodioxole moiety.

A large number of aromatic and heterocyclic compounds contain the dialkoxybenzene ring. The term dialkoxy is conventionally used in the place of methylenedioxy and o-dimethoxy groups. Mostly, the dialkoxy compounds are obtained by synthesis although many of them are frequently found as natural products. The simplest members of this class of compounds are represented by the veratrote (o-dimethoxybenzene) and catechol methylene ether (methylenedioxybenzene) which are often found as degradation products of naturally occurring substances such as alkaloids.

2.6.2. Biological review on 1,3-benzodioxole derivatives

This core is widely found in natural products like sesamol, piperonal, safrole, derrubone [Mays *et al.* 2010], among others, drugs and chemicals such as tadalafil, MDMA (3,4-methylenedioxymethamphetamine), and piperonyl butoxide [IARC Monographs 1976; Villegas *et al.* 2011; Mckenna *et al.* 1990]. Moreover, compounds that bear this group have diverse biological activities which includes anticancer [Leite *et al.* 2004], anticonvulsant [Aboul-Enein *et al.* 2012], anti-inflammatory [Lopes *et al.* 2012], antihypertensive [Taqvi *et al.* 2008], antioxidant [Himaja *et al.* 2011], antibacterial and antifungal [Sundararajan *et al.* 2014; 2014; Anandakumaran *et al.* 2016], GABA aminotransferase and/or GABA reuptake transporter inhibitor [Rao 2011] and others (**Figure 2.18.**) [Echevarria and Nascim ento 1999; Garraffo *et al.* 1993; Sekizawa *et al.* 1982; Stanfil *et al.* 2003; Yousif and Alies 2010].

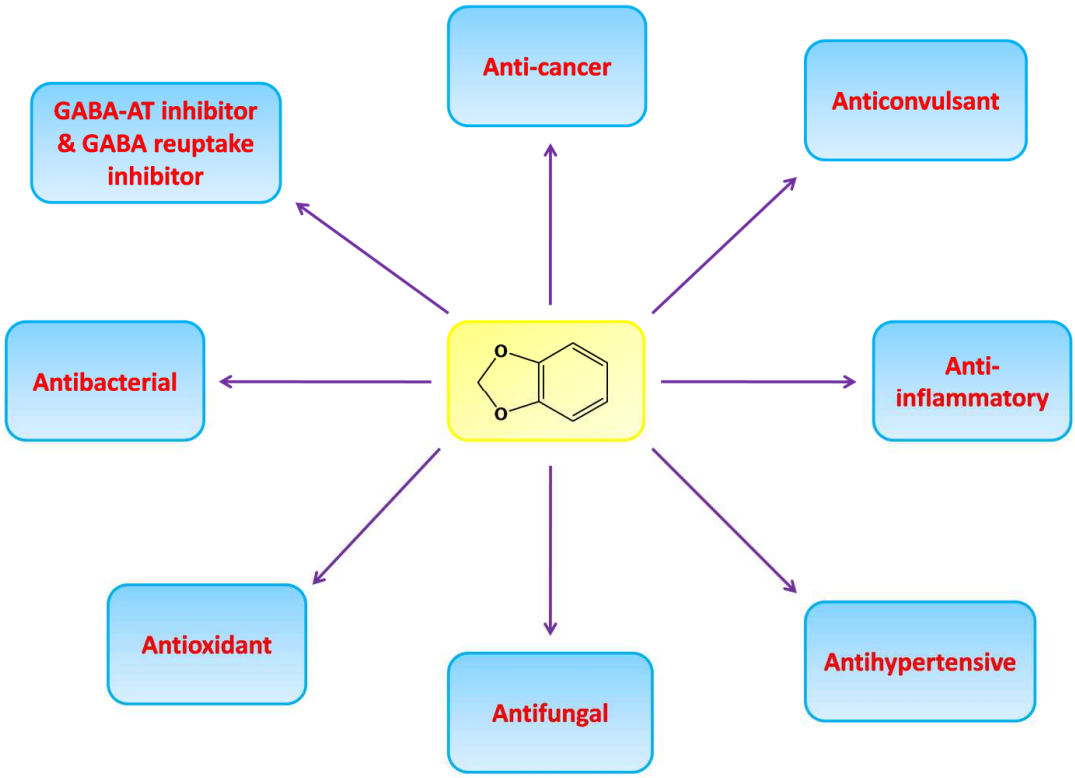


Figure 2.18. 1,3-Benzodioxole, a multifunctional nucleus

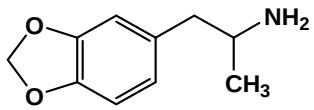
2.6.2.1. CNS activities

2.6.2.1.1. Psychostimulant and serotonin-norepinephrine-dopamine releasing agent and reuptake inhibitory activity

MDA (3,4-methylenedioxyamphetamine) **52** and its N-methyl analogue, MDMA (3,4-methylenedioxymethamphetamine) **53** are well known drugs that contain the 1,3-benzodioxole moiety. These drugs are known for their entactogenic, psychedelic and psychostimulant effects. Possession of MDA and MDMA is illegal in most countries. However, some limited exceptions exist for scientific and medical research.

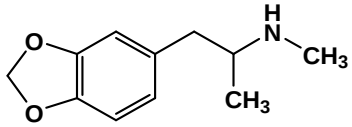
Pharmacologically, MDA acts as a serotonin-norepinephrine-dopamine releasing agent and reuptake inhibitor [Rothman and Baumann, 2006].

MDMA may have health benefits in certain mental disorders, but has potential adverse effects, such as neurotoxicity and cognitive impairment. More research is needed in order to determine if its potential usefulness in posttraumatic stress disorder (PTSD) treatment outweighs the risk of persistent neuropsychological harm to a patient [Meyer 2013; Parrott 2014].



Methylenedioxyamphetamine (MDA)

52

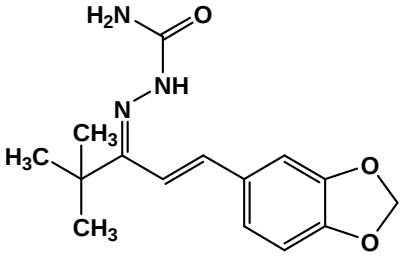


3,4-Methylenedioxymethamphetamine (MDMA)

53

2.6.2.1.2. Anticonvulsant activity

Aboul-Enein *et al.*, synthesized and evaluated a series of stiripentol (STP) analogues namely, 2-[(1E)-1-(1,3-benzodioxol-5-yl)-4,4-dimethylpent-1-en-3-ylidene]-N (aryl-/H)hydrazinecarboxamides, (±)-(5RS)-N-(aryl/H)-(1,3-benzodioxol-5-yl)-3-tertbutyl-4,5-dihydro-1H-pyrazole-1-carboxamides and (±)-[(5RS)-(1,3-benzodioxol-5-yl)-3-tertbutyl-4,5-dihydro-1H-pyrazol-1-yl](aryl)methanones for anticonvulsant activity. Compound **54** was found to be most active congeners in MES screen and **55** in scPTZ screen with ED_{50} values of 87 and 110 mg/kg, respectively, as compared to that of STP (ED_{50} = 277.7 and 115 mg/kg in MES and scPTZ, respectively) [Aboul-Enein *et al.* 2012].



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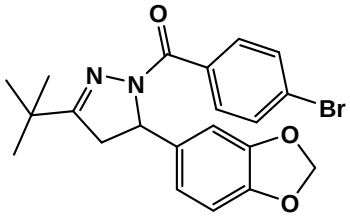
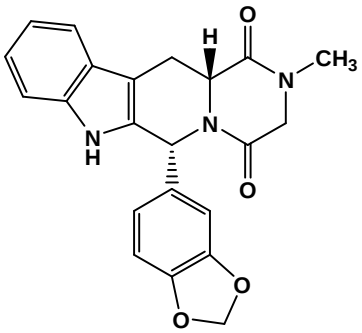


55

2.6.2.2. Miscellaneous activities

2.6.2.2.1. PDE5 inhibitory activity

Moreover, tadalafil **56** (**Figure 2.19.**), a PDE5 inhibitor, used in the treatment of erectile dysfunction (ED) and pulmonary arterial hypertension, also incorporates 1,3-benzodioxole moiety within its structure.

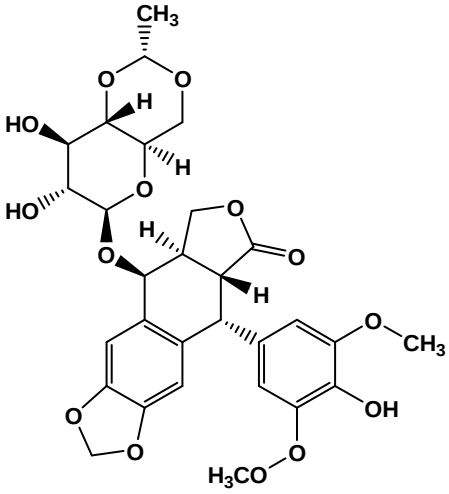


Tadalafil (56)

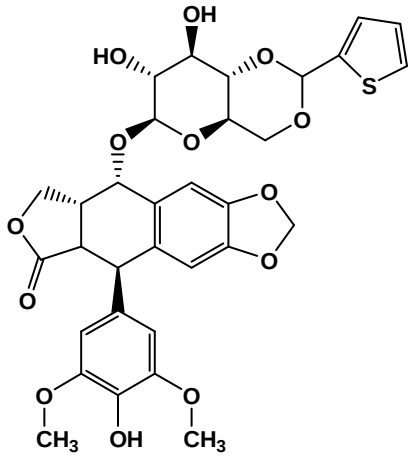
Figure 2.19. Structure of tadalafil incorporating 1,3-benzodioxole moiety

2.6.2.2.2. Antitumour activity

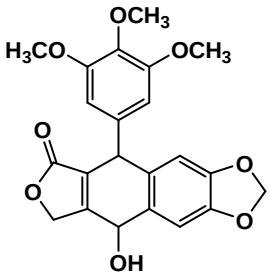
The 1,3-benzodioxole unit was identified in some clinical antitumor agents like etoposide **57** and teniposide **58** in addition to podophyllotoxin **59**, 4-azapodophyllotoxin **60** and thiazapodophyllotoxin **61** (**Figure 2.20.**).



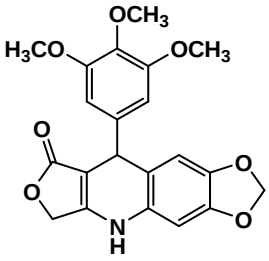
Etoposide (57)



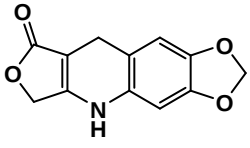
Teniposide (58)



Podophyllotoxin (59)



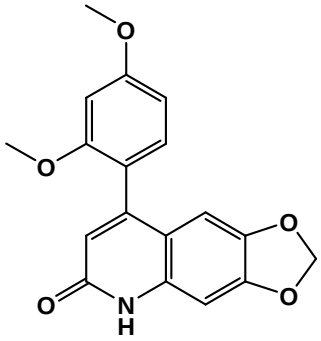
4-Azapodophyllotoxin (60)



Thiazapodophyllotoxin (61)

Figure 2.20. Antitumor agents possessing 1,3-benzodioxole nucleus

Further, novel 6,7-methylenedioxy-4-substituted phenylquinolin-2-one derivatives were synthesized and evaluated for *in-vitro* anticancer activity. Among the synthesized compounds, 6,7-methylenedioxy-4-(2,4-dimethoxyphenyl)quinolin-2(1H)-one (**62**) displayed potent cytotoxicity against several different tumor cell lines at a sub-micromolar level. Compound **62**, containing 2,4-dimethoxy substitution on the 4-phenyl ring, demonstrated potent antiproliferative activities with IC_{50} values of 0.4, 0.4, 0.4 and 0.9 μM against 2774, SKOV-3, HL-60 and H460, respectively [Chen *et al.* 2013].



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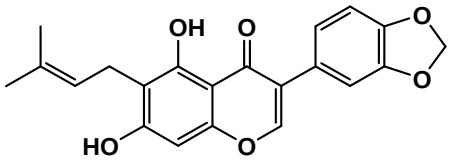
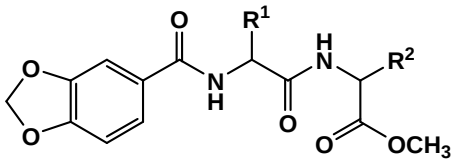


63

In 2007, a high-throughput screen identified derrubone **63** as a low micromolar inhibitor of Hsp90. The compound was found to exhibit an IC_{50} value of 11.9 ± 0.6 μM against MCF-7 [Hadden et al. 2007].

2.6.2.2.3. Antioxidant activity

A series of benzodioxole-5-carboxyl-amino acids and dipeptide methyl esters were synthesized and evaluated for the antioxidant activity. The compounds **64-65** exhibited significant antioxidant activity compared to the standard antioxidant BHT [Himaja *et al.* 2011].



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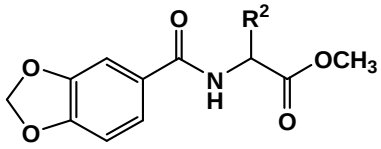
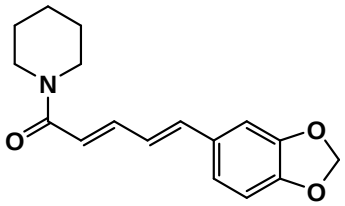


65

2.6.2.2.4. Blood pressure lowering and vasomodulator effects

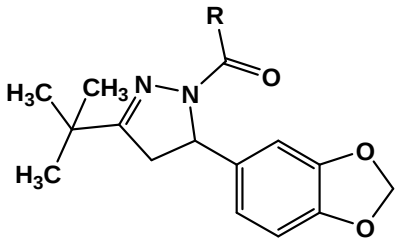
Piperine **66** was found to possess a blood pressure-lowering effect mediated possibly through calcium channel blockade (CCB), while consistent decrease in BP was restricted by associated vasoconstrictor effect [Taqvi *et al.* 2008].



66

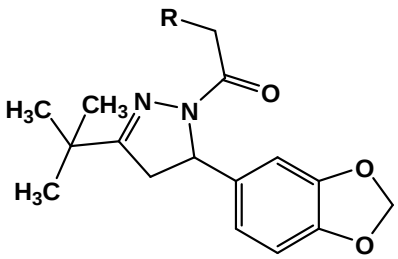
2.6.2.2.5. Antibacterial activity

Aboul-Enein *et al.* synthesized and screened a series of 5-(benzo[d][1,3]dioxol-5-yl)-3-tert-butyl-1-substituted-4,5-dihydropyrazole derivatives for antibacterial activity. Compound **67,** a pyrrolidinomethanone derivative, exhibited MICs of 80 and 110 nM respectively against the most sensitive bacteria Sarcina and Staphylococcus aureus. While hydroxypiperidinoethanone derivative **68** showed MIC of 90 nM for Sarcina [El-Behairy *et al.* 2015].



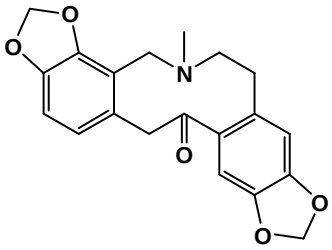
R = Pyrrolidine

67

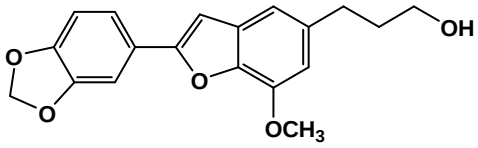


R = 4-Hydroxypiperidine

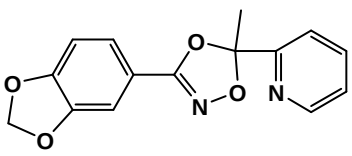
68



69 (Protopine)

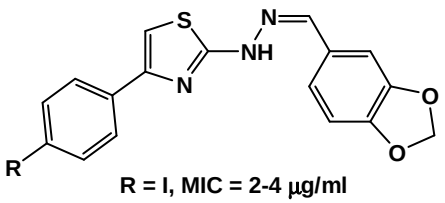


70 (Egonol)



IC_{50} = 1.0 μM

71



R = I, MIC = 2-4 μg/ml
R = CH_3, MIC = 0.125-2 μg/ml

72

Figure 2.21. Antimicrobial candidates containing 1,3-benzodioxole nucleus

During discovery of novel antibacterial agents, powerful activity has been displayed by natural molecules containing the 1,3-benzodioxole system for example protopine **69** [Carradori *et al.* 2012], egonol **70** [Emirdag-Ozturk *et al.* 2011] and also by several chemically synthesized antimicrobial candidates such as compounds **71** and **72** (**Figure 2.21.**) [Chimenti *et al.* 2011; Wani *et al.* 2011; Secci *et al.* 2012].

Because of its wide range of applications as mentioned above, 1,3-benzodioxole therefore represents an interesting template for medicinal chemistry.

2.7. Review on multi-target-directed ligand (MTDL) approach towards the discovery of anti-neurodegenerative agents

Among the various drug discovery methods, a very promising modern approach consists in designing multi-target-directed ligands (MTDLs). This method has been particularly developed for treatment of disorders associated with complex pathological mechanisms. Currently the most common multifactorial disorder is the neurodegenerative disease. There are evidences pointing to the role of oxidative stress, metal ion deregulation, inflammation and cell cycle regulatory failure, decreased level of acetylcholine, increased levels of amyloid β peptide (Aβ) in its pathogenesis causing the loss of neurons and synapses. There are many attractive targets for the development of anti-neurodegenerative drugs, and the multifactorial nature of this disease calls for multi-target-directed ligands which can be beneficial for the treatment of neurodegenerative diseases. Therefore, the multi-target directed ligand paradigm has been in the focus of growing attention by many research groups, which have developed a diversity of molecules acting on extremely dissimilar targets.

2.7.1. MTDLs targeting MAO and ChE

Multifunctional ligands able to simultaneously inhibit monoamine oxidases (MAOs) as well as cholinesterases (ChEs) have been already developed in the context of a MTDL approach, leading to the discovery of ladostigil (**73**), a brain selective molecule acting on different targets on the CNS which is in clinical trials for the treatment of AD in addition to **M30** (**74**) and **HLA20** (**75**).

A very successful approach of combined MAO/ChE inhibition came from the combination of the carbamate moiety of rivastigmine with the indoleamine moiety of rasagiline, a well-known MAO-B inhibitor, leading to the compound ladostigil (**73**) (**Figure 2.22.**) [Sterling *et al.* 2002]. Ladostigil was found inhibit both AChE and

butyrylcholinesterase (BuChE) for a longer time than the parent compound rivastigmine [Greig *et al.* 2005]. Additionally, ladostigil selectively inhibited both brain MAO-A and MAO-B thereby resulting in increase in the levels of noradrenaline, dopamine and serotonin, thus exerting an antidepressant effect. An important feature (aspect) of ladostigil is that it is selective for brain enzymes and hence it is devoid of the classical side effects observed after peripheral MAO inhibition. Besides, ladostigil has also been shown to retain the neuroprotective and anti-apoptotic properties observed in the rivastigmine and rasagiline [Weinstock *et al.* 2003; Yogev-Falach *et al.* 2002; Sagi *et al.* 2003]. Moreover, ladostigil also possesses a cognition enhancing activity and is the most advanced MTDL on its category as demonstrated by the promising results obtained from a phase 2 clinical trial [Youdim *et al.* 2006]. Two other clinical trials are underway to investigate its safety and efficacy in mild to moderate AD [http://clinical trials.gov/NCT01354691, http://clinicaltrials.gov/NCT014 29623].

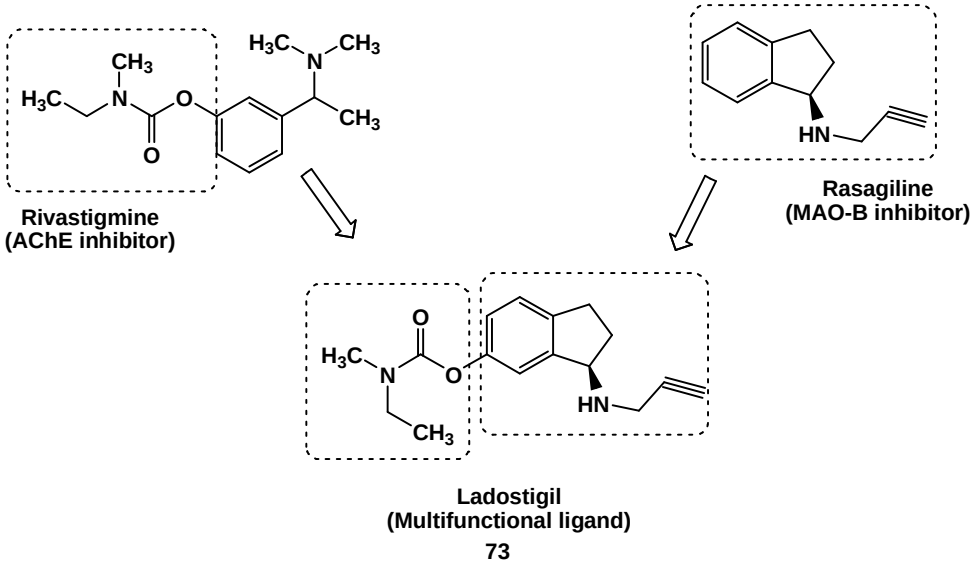


Figure 2.22. Dual MAO-ChE inhibitor created from the combination of rasagiline and rivastgmine

More recently, Bolea *et al.* reported a novel series of multipotent propargylamine-derived ChE/MAO inhibitors with a very promising profile [Bolea *et al.* 2011]. Their design strategy was based on the combination of N-benzylpiperidine moiety of donepezil with the indolyl propargylamine moiety of **PF9601N**, a potent propargylamine-containing MAO-B inhibitor possessing several neuroprotective properties (**Figure 2.23.**) [Prat *et al.* 2000; Cutillas *et al.* 2002; Pérez and Unzeta 2003; Perez *et al.* 2003; Battaglia *et al.*

2006; Sanz *et al.* 2008, 2009]. Compound **76** (**Figure 2.23.**) was found to potently inhibit both MAO-A and MAO-B. Interestingly, in addition to inhibiting both AChE and BuChE, **76** was also found to inhibit $A\beta_{1-42}$ self-induced aggregation as well as AChE induced $A\beta_{1-40}$ aggregation indicating that **76** interacted with the peripheral anionic site (PAS) of AChE which is responsible for mediating the amyloid-β (Aβ) peptide proaggregating action of AChE [Inestrosa *et al.* 1996; De Ferrari *et al.* 2001; Dinamarca *et al.* 2010]. Thus compound **76** retained the anti-apoptotic and antioxidant properties of the parent compound **PF9601N** and possessed a favourable blood–brain barrier crossing capability. These findings suggested that compound **76** could be a new and promising future multitarget drug candidate for the treatment of the multifactorial nature of AD.

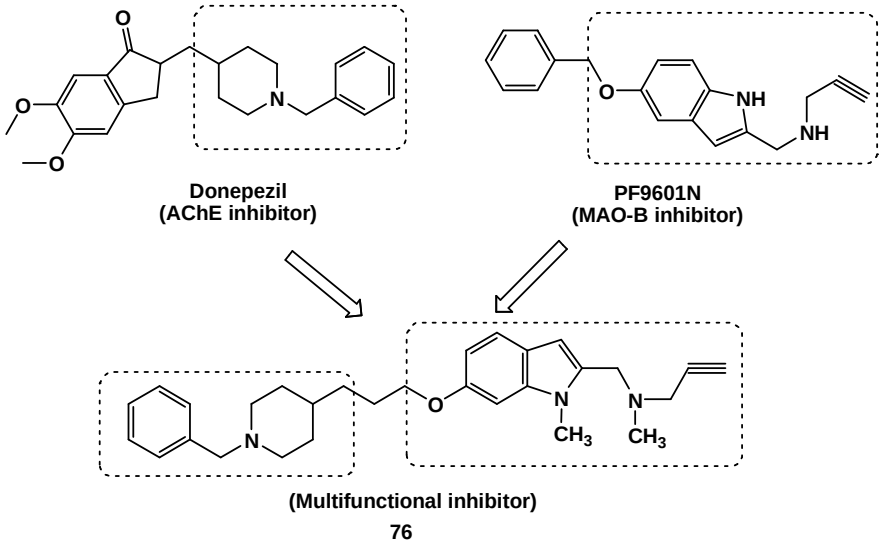


Figure 2.23. Dual MAO-AChE-Aβ inhibitor created from the combination of donepezil and PF9601N

2.7.2. MTDLs targeting MAO and iron

Literatures have reported the presence of excessive concentration of iron at the sites of neuronal degeneration [Mattson, 2004]. Moreover, iron contributes to Aβ aggregation causing neuronal degeneration due to the stimulation of oxidative stress [Yoshiije *et al.* 2001]. There exists a link between high concentration of iron and MAO activity and their connection to the production of ROS [Shoham and Youdim 2000]. Youdim and co-workers synthesized compounds with multifunctional activity against iron chelation and MAO by the combination of iron-chelating and antioxidant scaffold of VK-28 and N-propargylamine moiety of rasagiline [Zheng *et al.* 2010] resulting in compounds M30

(**74**) and HLA20 (**75**) (**Figure 2.24.**) possessing iron-chelating activity similar to VK28, but with higher brain permeability [Zheng *et al.* 2005]. Both the compounds possessed neuroprotective properties similar to rasagiline and potently inhibited the iron induced membrane lipid peroxidation [Youdim *et al.* 2004; Zheng *et al.* 2010]. In addition to the above activities, M30 (**74**) was also found to selectively inhibit brain MAO-A and MAO-B enzymes, thereby increasing the concentration of serotonin, dopamine and adrenaline, thus exerting antidepressant action besides preventing potentiation of tyramine-induced cardiovascular activity [Gal *et al.* 2005]. Moreover, M30 (**74**) also caused inhibition of the Aβ aggregation provoked (induced) by metals and reduced Aβ formation [Amit *et al.* 2008; Avramovich-Tirosh *et al.* 2007].

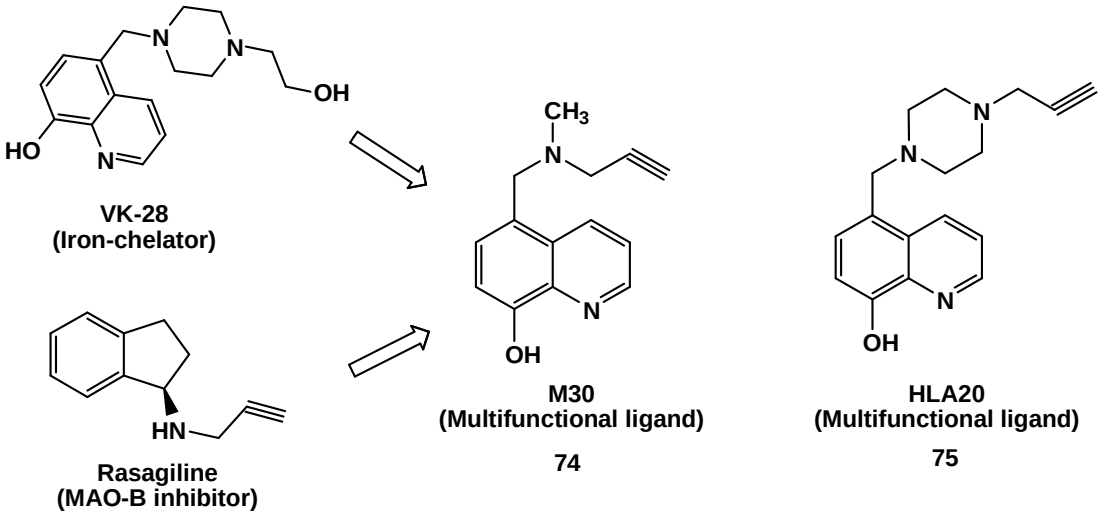


Figure 2.24. Dual MAO-Iron chelation inhibitors M30 (**74**) and HLA20 (**75**) created from the combination of rasagiline and VK-28

2.7.3. MTDLs targeting MAO, AChE and iron

With a view to discover multifunctional ligands acting against MAO, AChE and iron-chelation, Zheng *et al.* in 2010, developed M30D (**77**) (**Figure 2.25.**) and HLA20D (**78**) (**Figure 2.26.**) by incorporating the carbamate moiety of rivastigmine into the structure of M30 and HLA20 respectively. Both the compounds M30D (**77**) and HLA20D (**78**) were found to possess, in addition to MAO inhibition and iron-chelating activities of the parent compounds M30 (**74**) and HLA20 (**75**), an interesting AChE inhibition activity as well [Zheng *et al.* 2010]. The mechanism of action is based on the idea that the iron chelation ability is triggered after the inhibition of AChE which results in the release of the active chelators M30 (**74**) and HLA20 (**75**).

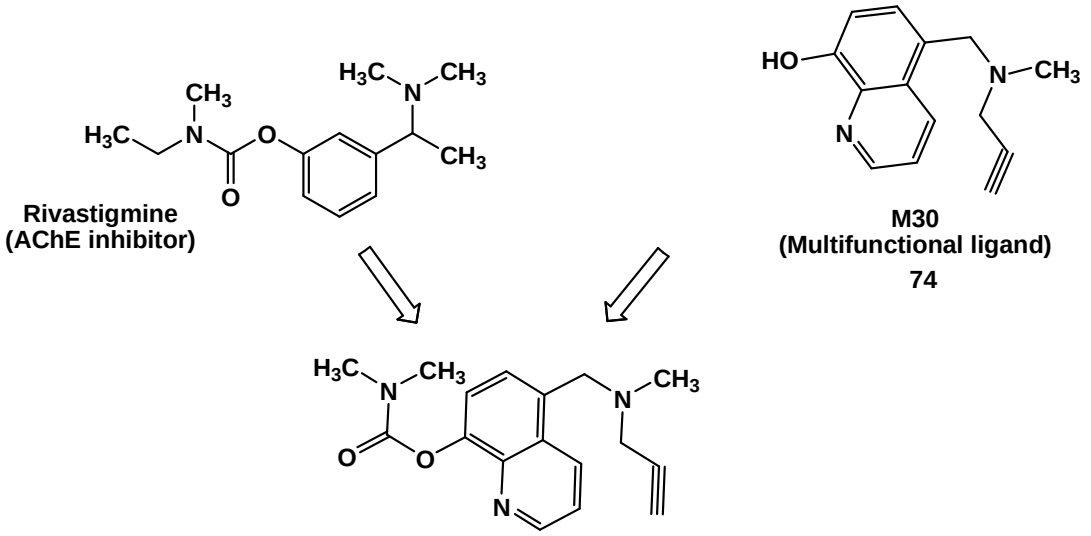


Figure 2.25. Multifunctional ligand M30D (**77**) created by combining rivastigmine and M30 (**74**)

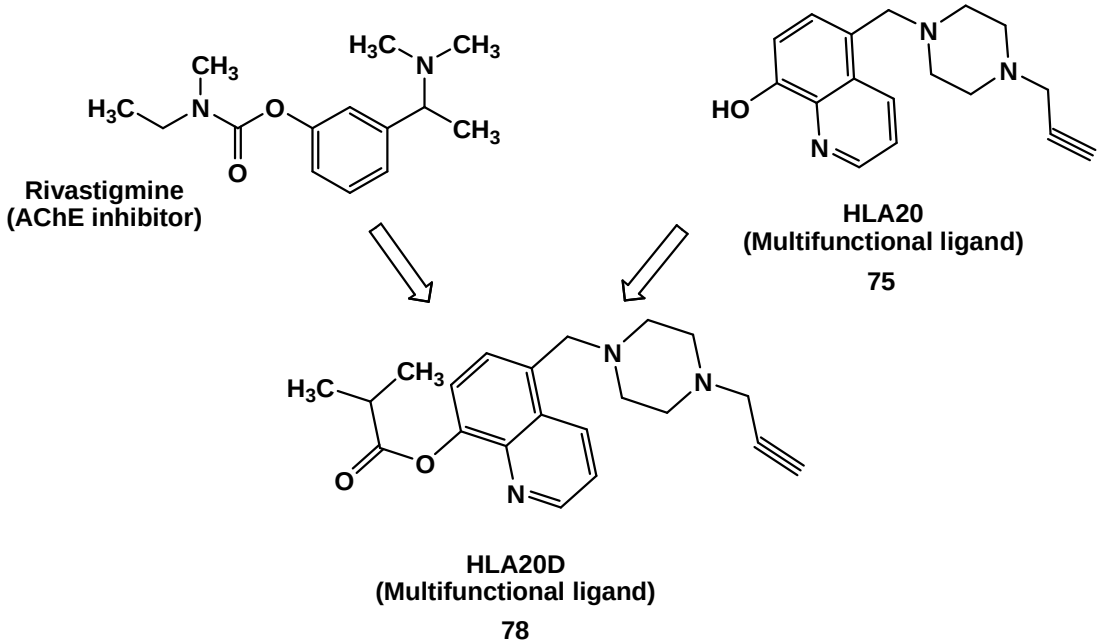


Figure 2.26. Multifunctional ligand HLA20D (**78**) created by combining rivastigmine and HLA20 (**75**)

In view of the above facts, oxidative stress being regarded as an early event in the pathogenesis of NDDs, and thus targeting the source of reactive oxygen species (ROS)

early in the progression of the disease is a matter of interest. In this context, MAO appears as a key target and AChE as a secondary target to be considered when designing MTDLs against NDDs, not only due to the increased amine neurotransmission, but also because of the reduction of the neurotoxic products of its catalytic activity.

Particularly, ligands incorporated with hydrazone skeleton and semicarbazone scaffold and 3-hydroxy-3-phenacyloxindole analogues of isatin may possess additional benefits due to the demonstrated neuroprotective, neurorescue and other biological properties.

Thus, it was thought worthwhile to synthesize some ligands bearing N, S, and O containing heterocyclic nucleus such as thiazole, benzothiazole, 1,3-benzodioxole and isatin. The present thesis deals with the design, synthesis and evaluation of some heterocyclic compounds as neurotherapeutic agents.