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REVIEW

Antioxidant Activity of Piperazine Compounds: A Brief Review

SHAHEEN BEGUM*, M.S. RASHIDA ANJUM, G. POOJITHA HARISREE, N. SIVALAKSHMI, P. PRIYANKA and K. BHARATHI

Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam, Tirupati-517502, India

*Corresponding author: E-mail: shaheen.pharmchem@gmail.com

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Piperazine ring is found in several potent antioxidant molecules. Literature survey revealed that the piperazine ring has been coupled to different heterocyclic rings such as quinoline, pyridine, pyrazine, azole, 1,3,4-oxadiazole, 1,4-benzodioxane, pyrrolidinone, benzimidazole, pyrazine benzimidazole to obtain compounds with good antioxidant activity. It is found that the natural compounds like α-lipoic acid, methylxanthine, berberine, sarsasapogenin, chrysin, chromen-4-one, co-enzyme Q when attached to piperazine ring, antioxidant activity was improved. In the present article, piperazine containing antioxidant molecules were reviewed.

Keywords: Piperazine, Antioxidant, Free radical scavenging.

INTRODUCTION

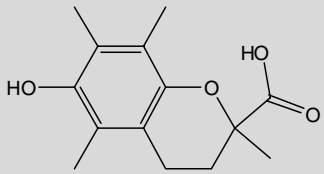
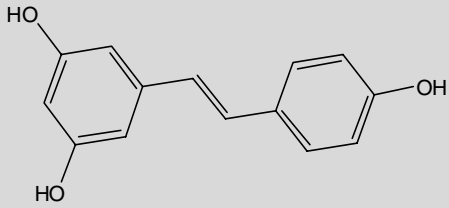
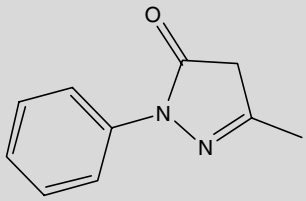
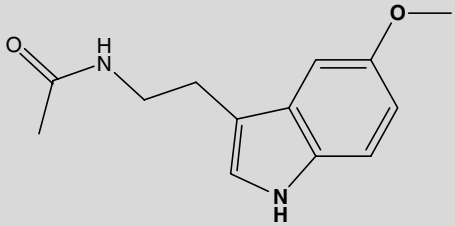
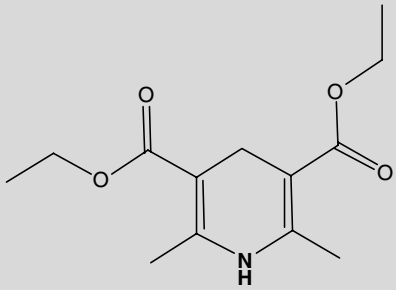
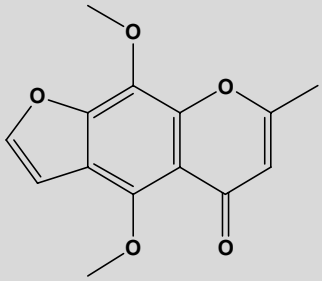
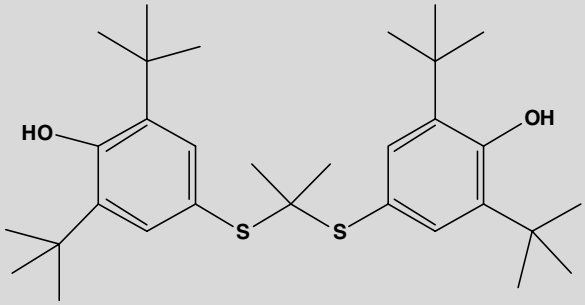
Antioxidants play a key role in the progress of several pathological conditions such as inflammation, pain, diabetes, neurodegenerative diseases and organ toxicity [1-3]. Of the several natural and synthetic antioxidants, few like vitamin C, vitamin E, quercetin, *N*-acetyl cysteine, carnosine, lipoic acid are endowed with potential therapeutic benefits [4]. Periodical reviews on antioxidants and their therapeutic applications imply significance of these molecules in drug development [5-7]. In general amino and hydroxy groups show radical scavenging ability and are potent antioxidants. In the literature, SAR was mentioned for natural antioxidants (presence of hydroxy group and conjugating ring system, presence of catechol moiety) while for other antioxidants no such studies are available [8]. Several antioxidant compounds contain heterocyclic rings in their structure such as indole, 1,4-dihydropyridine, benzopyran, piperidine, piperazine [9-17] (Table-1).

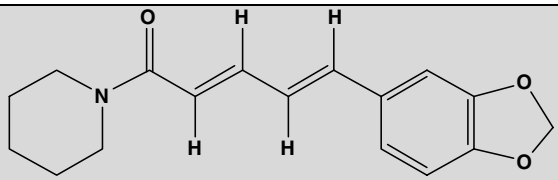
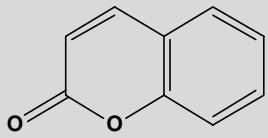
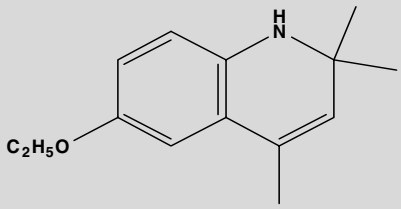
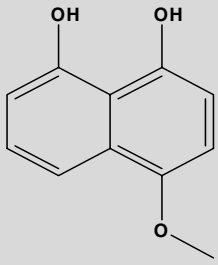
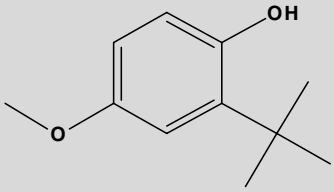
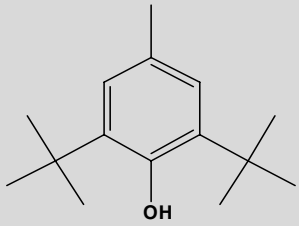
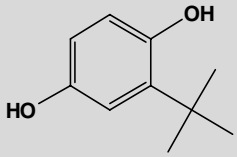
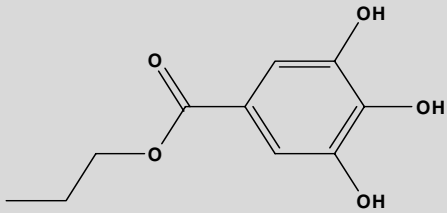
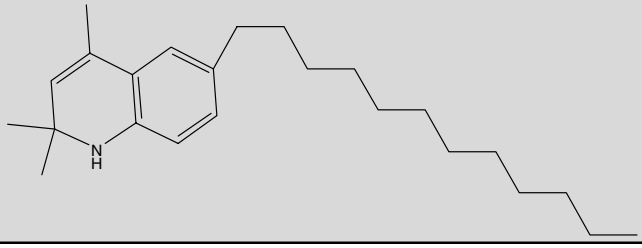
Piperazine nucleus has emerged as a privileged core due to its presence in various pharmacological agents [18]. Piperazine in its unsubstituted form has anthelmintic property and acts as GABA-mimetic agent and causes muscle blockade in worms [19]. This nucleus can be substituted at both ends with aryl/heteroaryl or alkyl groups and can be linked to give Mannich or Schiffs bases. *N*-Aryl piperazine scaffolds are extensively studied as CNS agents [20]. Piperazine ferulate is used in China for treating glomerulonephritis. The exact mechanism of this compound is not clear, but it partially inhibits the growth of connective tissue growth factor in glomeruli and also decreases oxidative stress [21,22]. Earlier studies revealed that when piperazine ring was tethered with different heterocyclics or natural compounds antioxidant activity of the parent compound was improved. The availability of two lone pairs of electrons at nitrogen atoms in piperazine might play a key role in improving free radical scavenging ability [23,24]. The present review might be used to design and develop potential antioxidant agents.

Piperazine derivatives linked to pyrido[3,2-*e*]-1,2-thiazine-1,1-dioxide (Fig.1) were synthesized for CNS pharmacological screening in animal models. The compounds were also evaluated *in vitro* by using the total peroxyl radical-trapping antioxidant potential (TRAP) method. These hybrids of piperazine-pyridothiazines exhibited good analgesic activity and anti-inflammatory activity. The antioxidant potential of these compounds is similar to that of *N*-acetyl cysteine used as a standard compound. The free radical scavenging ability was attributed to the presence of β-dicarbonyl functionality in the final structures [25].

Diphenylpropylpiperazine derivatives containing thio or amino propanol moiety substituted by phenyl or benzyl group

TABLE-1
FEW ANTIOXIDANTS CONTAINING ARYL/HETEROARYL RING

Name	Structure	Aryl/heteroaryl ring present	Natural/synthetic
Trolox		Chromane ring	Synthetic
Resveratrol		Stillbenoid	Natural
Edaravone		Pyrazolone	Synthetic
Melatonine		Indole	Natural
Diludine		1,4-dihydropyridine (1,4-DHP)	Synthetic
Khelline		Benzfuran	Natural
Probucol		Bisphenol	Natural

Piperine		Piperidine	Natural
Coumarin		Coumarin	Natural
Ethoxyquin		Quinoline	Synthetic
4-Methoxy1,8-naphthalene diol		Naphthalene-diol	Natural
Butylatedhydroxyanisole		Phenol	Synthetic
Butylatedhydroxytoulene		Phenol	Synthetic
Tert-Butylhydroquinone		Phenol	Synthetic
Propyl gallate		Triphenol	Synthetic
6-Dodecyl-2,2,4-trimethyl-1,2-dihydroquinoline		Quinoline	Synthetic

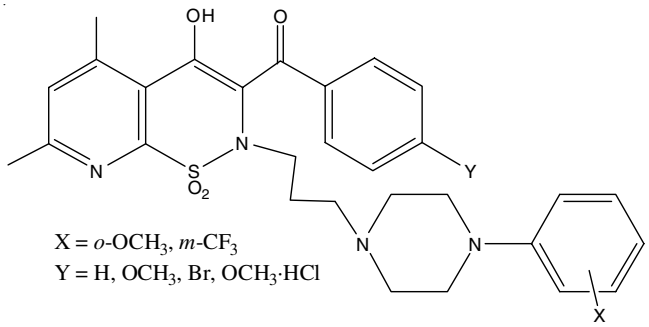


Fig. 1. Structure of piperazine linked to pyrido[3,2-*e*]-1,2-thiazine-1,1-dioxide

(Fig. 2) were synthesized and evaluated for calcium antagonistic and antioxidant activities. Among them phenylamino compound and benzylamino compound also possessed potent inhibitory activities against auto-oxidative lipid peroxidation in canine brain homogenates. The phenylthio compound without any substitution showed an IC_{50} value of 15 μM and it was equivalent in activity to flunarizine but less potent than α-tocopherol (IC_{50}, 1.5 μM). The study concluded that modifications of aminopropanol moiety showed significant influence on biological activities when compared to thiopropanol group. Replacement of the hydroxy group with methoxy or acetoxy group leads to less active compounds [26].

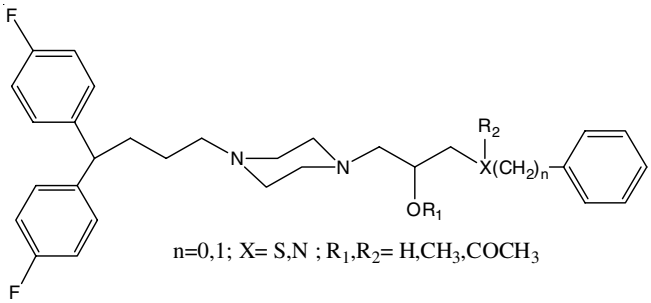


Fig. 2. Structure of diphenylpropylpiperazine derivatives

Geronikaki *et al*. [27] reported a 4,5-disubstituted-thizoyl amides (Fig. 3) containing structural motifs like 4-hydroxypiperidine/4-*N*-methyl piperazine exhibited modest antioxidant activity in hydroxyl radical scavenging and DPPH assays. These compounds were designed for anti-inflammatory activity and observed significant lipooxygenase (LOX) inhibition with few of the derivatives.

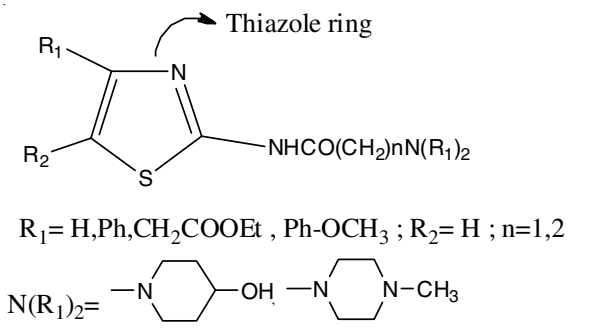


Fig. 3. Structure of thiazole linked piperazines

Carvedilol, (Fig. 4) an antihypertensive agent exerts significant antioxidant activity in different animal models. By replacing the carbazole ring with a phenyl group and by introducing the piperazine ring in the aliphatic chain of carvedilol, few compounds (Fig. 5) were synthesized and evaluated for antihypertensive and antioxidant activity. The results of the study showed that 2,6-dimethyl derivative exhibited significant hypotensive activity in normotensive rats and promising results in ferric reducing ability (FRAP), superoxide dismutase (SOD) and catalase (CAT) assays. The compound with 3-CH_3 and 4-Cl groups showed significant antioxidant activity when compared to the reference compounds Trolox and resveratrol [28].

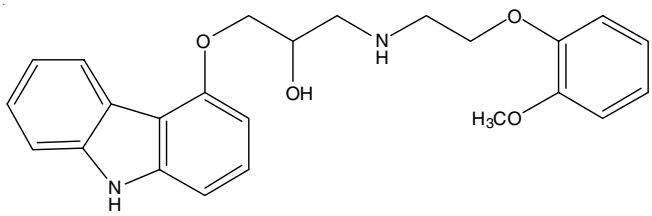


Fig. 4. Carvedilol

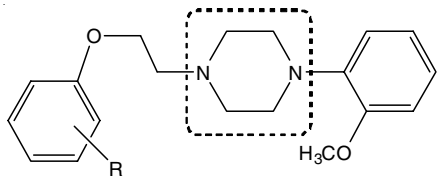


Fig. 5. Structure of piperazine derivatives

Trimetazidine (Fig. 6) exhibits cardioprotective activity and used in the treatment of stable angina. Research has shown that this core nucleus is endowed with partial fatty acid oxidation inhibitory activity. To enhance the antioxidant profile, trimetazidine was structurally modified by introducing pyroline or phenyl substituted pyroline (Fig. 7) at piperazinyl hydrogen and as expected, antioxidant activity was found to be improved. The final compounds showed improved cardioprotective activities and this improvement was found to be partly due to their antioxidant ability [29].

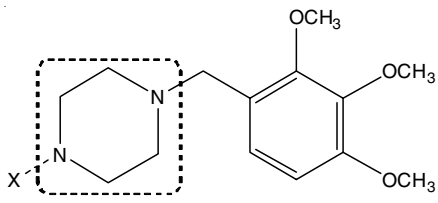


Fig. 6. Structure of trimetazidine

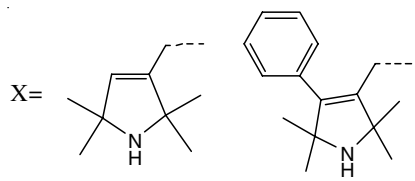
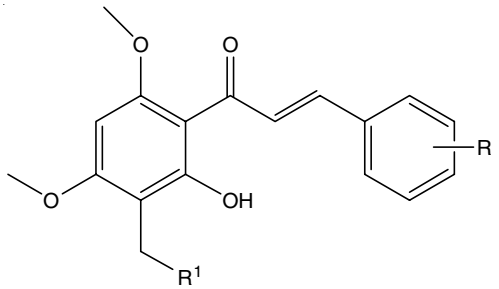


Fig. 7. Structural modifications of trimetazidine

Chalcones are bioactive scaffolds with a broad range of activities. Incorporation of piperazine ring on one of the aryl rings in the form of Mannich base (Fig. 8), moderately improved the antioxidant profile of the synthesized compounds. Moreover, novel compounds were highly effective against the proinflammatory enzyme (COX-2). The compound bearing 3-Br and piperazine substitution showed more potent activity with % DPPH reduction of 37% than natural chalcone (16.67%), but it was less potent than quercetin (86.30%) [30].

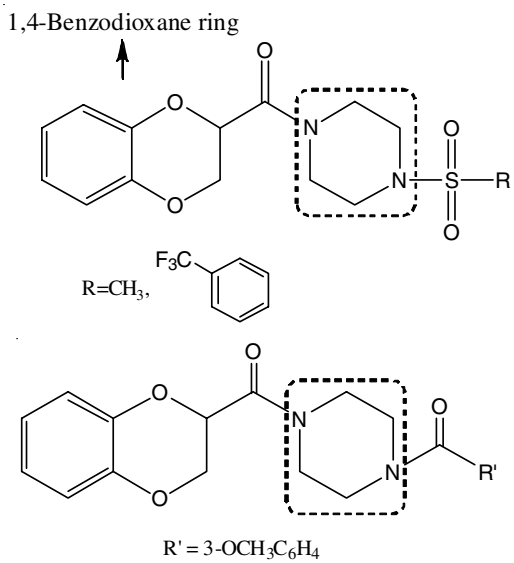


R = 3-Br, 2-F, 2-Br, 3-F, 2-Cl, 3-Cl

R^1 = piperazine, morpholine, pyrrolidine, piperidine

Fig. 8. Structure of modified chalcones

When 1,4-benzodioxane ring and piperazine ring were tethered (Fig. 9) antibacterial, antifungal, antioxidant potencies were enhanced. Compound with trifluoromethyl phenyl ring demonstrated significant antimicrobial activity and 3-methoxybenzoyl compound showed moderate antioxidant activity (IC_{50} value of 35.2 µg/mL) when compared to the standard drug ascorbic acid (IC_{50} ,10.62 µg/mL) in DPPH assay [31].



R' = 3-$OCH_3C_6H_4$

Fig. 9. Structure of piperazines linked to 1,4-benzodioxane ring

Salga *et al*. [32] designed and synthesized novel Schiff's bases of 1-(2-ketoiminoethyl)piperazines as anti-Alzheimer agents. While investigating inhibitory activities on human acetylcholinesterase enzyme, compounds were also screened for antioxidant activities. Amongst all, dihydroxy phenyl derivative (Fig. 10) exhibited highest human acetylcholinesterase inhibition and good antioxidant activity in DPPH assay (IC_{50} value of 25±1.24 µg/mL) using ascorbic acid as standard (IC_{50}, 1.4 ± 0.71 µg/mL) while pyridinyl derivative (Fig. 10) revealed the highest activity with IC_{50} of 1464.7 ± 5.2 µM in the FRAP assay when compared to ascorbic acid (IC_{50}, 1552.7 ± 4.2) and BHT (IC_{50}, 187.3 ± 2.6) as standards.

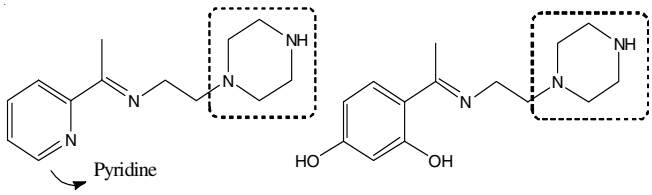
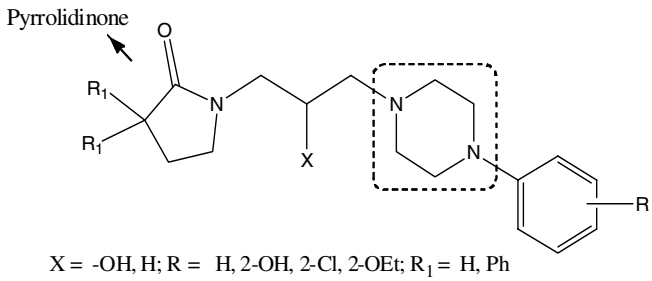


Fig. 10. Structure of Schiff's bases of 1-(2-ketoiminoethyl)piperazines

Sapa *et al*. [33] synthesized piperazine derivatives by attaching substituted phenyl piperazine to the nitrogen of pyrrolidin-2-one scaffold *via* propyl or 2-hydroxy propyl chain (Fig. 11). Pyrrolidinones exhibit a potent adrenolytic and antiarrhythmic properties. The synthesized compounds were also tested for antiarrhythmic and as well as for antioxidant activity. Among them, EP-40, 2-hydroxy derivative showed excellent antiarrhythmic activity and significant antioxidant activity. Antioxidant activity was measured as rates of membrane lipid peroxidation in rat liver homogenate (TBARS formation). Out of the tested compounds, the compound containing 2-ethoxy substitution significantly inhibited Fe^{2+} initiated lipid peroxidation [33].



X = -OH, H; R = H, 2-OH, 2-Cl, 2-OEt; R_1 = H, Ph

Fig. 11. Structure of piperazines linked to pyrrolidinone

Piperamide derivatives were found to act as MAO inhibitors and are endowed with anticonvulsant ability. A series of piperamides were synthesized with various substituted piperidine and piperazines (Fig. 12) and evaluated for antibacterial, antifungal, antidepressant and antioxidant activities. Piperazine bearing compounds demonstrated modest antioxidant activity in DPPH and superoxide radical scavenging assays. The compound bearing substituted hydroxyl group attached to the piperidine ring showed the highest activity (IC_{50}, 8.3 ± 0.02 µg/mL). Piperazine substituted compound exhibited moderate activity with IC_{50} value of 20.1 ± 0.07 µg/mL in comparison with the standard ascorbic acid (IC_{50}, 12.6 ± 0.43 µg/mL) in DPPH assay while in superoxide radical scavenging assay it is less potent (IC_{50}, 38.4 ± 0.04 µg/mL) than BHA (IC_{50}, 13.4 ± 0.29 µg/mL). Acetyl substituted piperazine compound showed good activity (IC_{50}, 21.9 ± 0.16 µg/mL) in superoxide radical scavenging assay, but less active (IC_{50}, 23.2 ± 0.16 µg/mL) in DPPH assay [34].

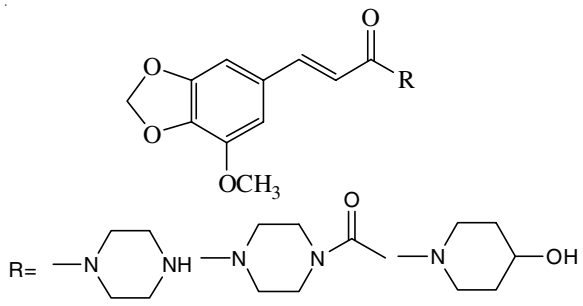
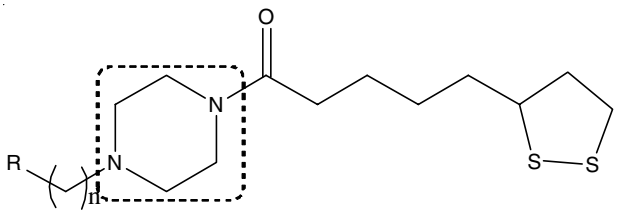


Fig. 12. Structure of piperamides

Sigma (σ) receptors, classified as σ1 and σ2, belong to the opioid class of receptors. To produce strong analgesic agents, Prezzavento *et al*. [35] designed novel compounds by coupling α-lipoyl moiety (antioxidant and neuroprotective agent) and various substituted piperazine and piperidines (Fig. 13). These bifunctional compounds showed selectivity towards σ-1 receptors and significant antioxidant activity in rat liver and brain mitochondria. Among all, benzyl piperazinyl analog displayed high affinity and selectivity for σ-1 receptors [35].



$R=CH_3, C_6H_{11}, C_6H_5$; n = 0, 1, 2, 3

Fig. 13. Structure of piperazines linked to α-lipoic acid

While investigating the neuroprotective effects of CXC137 (Fig. 14), a tetramethylpyrazinepiperazine derivative, researchers have screened its antioxidant activity. CXC137 demonstrated significant antioxidant superoxide dismutase activity and decreased lipid peroxidation. CXC137 also showed a modest antioxidant effect against DPPH. The % radical scavenging activity was found to be 39% at 120 µmol/mL while for the standards vitamin E and tetramethyl pyrazine, the values were 80% and 38%, respectively [36].

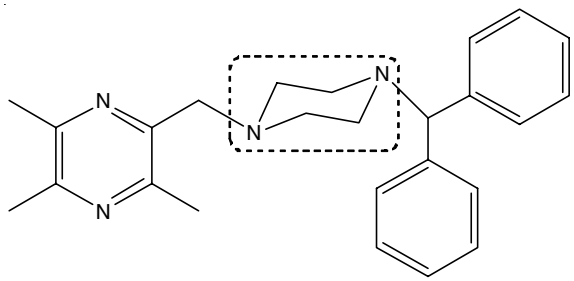


Fig. 14. Structure of CXC137

Andonova and coworkers [37] synthesized hybrid molecules containing methylxanthine and aryl/aralkyl substituted piperazine derivatives (Fig. 15) and screened using DPPH, ABTS and FRAP methods. Substituent groups were introduced on N-4 position of methylxanthine. The highest antioxidant activity

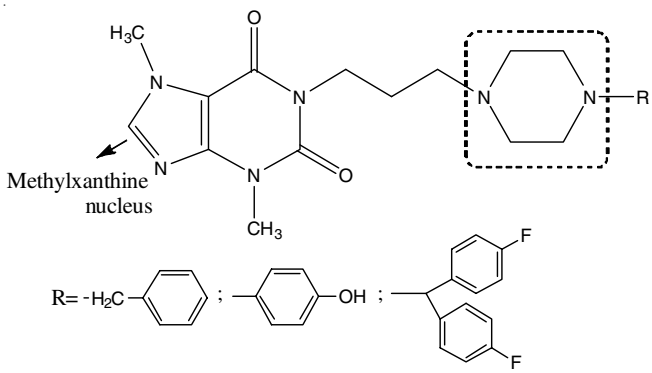
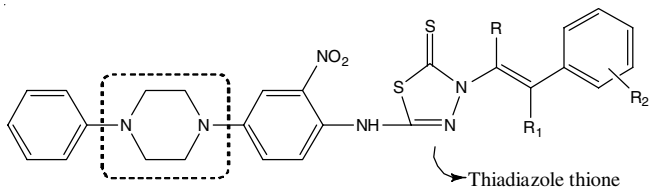


Fig. 15. Structure of piperazines linked to methylxanthine

was demonstrated by a compound containing hydroxyl group in all the assays like DPPH (IC_{50}, 189.4224 µmol/L^2), ABTS (IC_{50}, 3.45 µmol/L^2) and FRAP (IC50, 173.99 ± 1.50 µmol/L^2) when compared with the standard BHT (IC_{50} values, 113.17 , 26.29, 23.26 ± 0.45 µmol/L^2) in respective methods.

A new class of thiadiazole having a combination of Schiff base and Mannich base containing *N*-phenyl piperazine moiety (Fig. 16) was synthesized [38]. Antioxidant activity of the methanolic solution of the synthesized compound was determined by reducing power assay and H_2O_2 scavenging activity. The synthesized compounds were also screened for antibacterial activity. The maximum reducing potential was observed for the compound with morpholino and 4-hydroxy-3-methoxy benzylidene substitution in reducing power assay. The same compound exhibited good %scavenging activity when compared to the standard BHT in hydrogen peroxide scavenging assay.



R = Anisidino/morpholino/piperidino; R_1 = H, CH_3;
R_2 = 4-Hydroxy-3-methoxy-benzalidene, 4-hydroxy-benzalidene

Fig. 16. Structure of piperazine derivatives

1,3,4-Oxadiazole linked piperazine sulphonamides (Fig. 17) were screened for antioxidant activity by DPPH, OH• and NO• methods. Compound with oxydibenzene group showed significant radical scavenging activity with 93.8, 93.9 and 95.8% in comparison with BHT (96.8, 94.9 and 96.9%) in DPPH, nitric oxide and hydroxyl radical scavenging assays, respectively [39].

Wang *et al*. [40] designed and synthesized coenzyme Q_{10} analogs (substituted at C-6 position with various groups) (Fig. 18). *in vitro* Antioxidant activity was evaluated by employing DPPH assay. Promising antioxidant activity was observed for the compound bearing CH_2-*N*-benzoyl piperazine substitution at C-6 position which exhibited IC_{50} value of 193.84 µM when compared to coenzyme Q_{10}, IC_{50}, 1211.54 µMin DPPH assay [40].

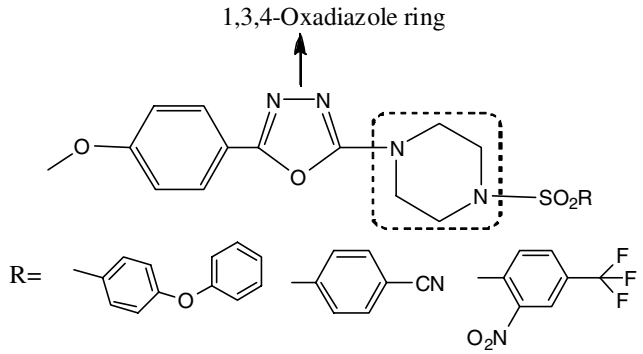


Fig. 17. Structure of piperazines linked to 1,3,4-oxadiazole ring

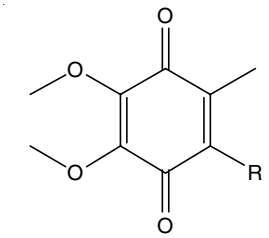


Fig. 18. Structure of coenzyme Q_{10} analogs

Al-Ghorbani *et al*. [41] designed and synthesized a series of quinolone/pyridine linked piperazine derivatives (Fig. 19). Because of anti-inflammatory potential and inhibition of PLA2 activity, quinoline and pyridine were selected while piperazine scaffold was chosen due to its ability to act as an antioxidant agent. The analogs were evaluated for *in vitro* antioxidant activity against DPPH and ferrous ion radical scavenging assays and anti-inflammatory activity. The compound with pyridine and nitro phenyl group showed the highest activity (3.5 µg/mL) in DPPH assay and the activity was higher than standard BHT (4.4 µg/mL)while in ferrous ion radical scavenging assay the compounds bearing methyl quinolone and phenyl group (7.6 µg/mL); quinolone and methyl group (6.2 µg/mL) substitutions showed higher activity than standard BHT (9.6 µg/mL) [41].

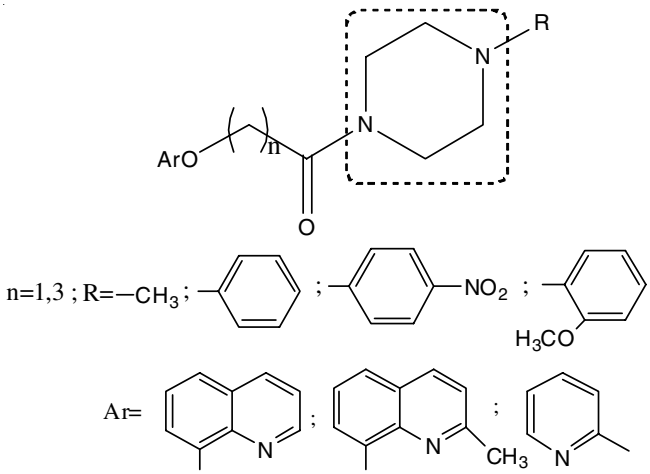


Fig. 19. Structure of piperazines linked to quinolone/pyridine

Novel series of pyrazine-2-carboxylic acid derivatives (Fig. 20) was synthesized by treating substituted pyrazine-2-carboxylic acid with various piperazines in the presence of propyl phosphoric anhydride (T3P). When tested for antioxidant activity in ABTS and DPPH assays, a compound having amino or amino pyrimidinyl groups showed good activity (IC_{50} values,6.53 and 60.37 µg/mL) in comparison to ascorbic acid (IC_{50}, 30.62 and 10.11 µg/mL) [42].

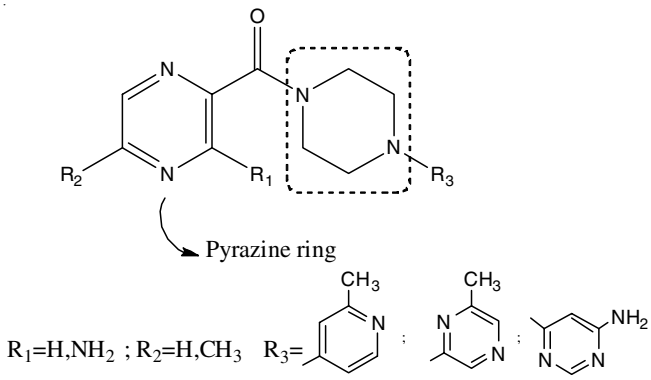


Fig. 20. Structure of piperazines linked to pyrazine ring

Novel azo dyes containing benzyl piperazine (Fig. 21) were synthesized and investigated for antioxidant activity using the FRAP method. Amongst all, the compound with acetamido group showed promising activity (155 ± 2.5 µM) [43]. In continuation, Mohammadi *et al*. [44] also synthesized few azo dyes (Fig. 22) and investigated their antioxidant activity against the FRAP method and their dyeing properties. The compound with benzothiazole group showed excellent antioxidant activity [44].

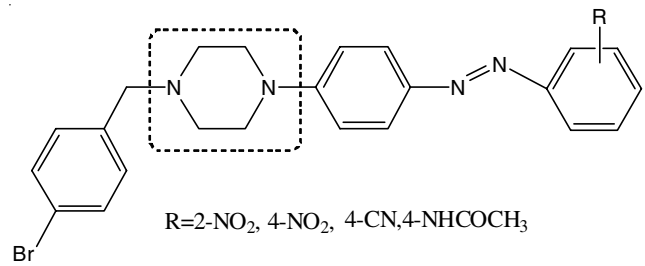


Fig. 21. Structure of azo derivatives linked to piperazine moiety

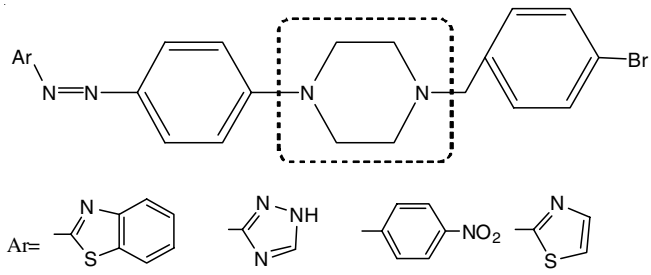


Fig. 22. Structure of azo derivatives containing piperazine

trans-2,5-Dimethyl piperazine-1,4-diium pentachlorobismutate, a hybrid of organic-inorganic compound was synthesized by Essid *et al*. [45]. Investigation of antioxidant activity in DPPH, hydroxyl radical, FRAPS and FIC methods revealed significant antioxidant activity of hybrid molecule [45]. Gatfaoui *et al*. [46] synthesized 1-methyl piperazine-1,4-diium-*bis*nitrate (MPN) and determined antioxidant properties *via* DPPH, ABTS, hydroxyl radical scavenging and FRP assays.

The compound exhibited significant activity with IC_{50} values 0.96, 1.11, 1.15 and 0.81 mg/ML in comparison with the ascorbic acid (IC_{50}: 0.476, 0.73 , 0.68 and 0.545 mg/ML) by DPPH, ABTS, hydroxyl radical scavenging and FRP methods, respectively.

Literature evidences a strong correlation between inflammation and the generation of free radicals at the site. Researchers have focused not only on the anti-inflammatory activity of a molecule but also it's capacity to stabilize free radicals. In an attempt to design potent antiinflammatory agents, Shankar *et al.* [47] synthesized pyrazine benzimidazole-piperazine/pyrazine conjugates (Fig. 23) and screened for *in vitro* anti-inflammatory activity against COX-2 and antioxidant activity by DPPH assay. Compounds with isopropyl piperazine or *N*-phenyl piperazine side chain exhibited appreciable antioxidant activity with IC_{50} values of 21.7 ± 0.45, 38.9 ± 0.62 µM when compared with the standard, ascorbic acid 19.9 ± 0.69 µM in DPPH radical scavenging assay [47].

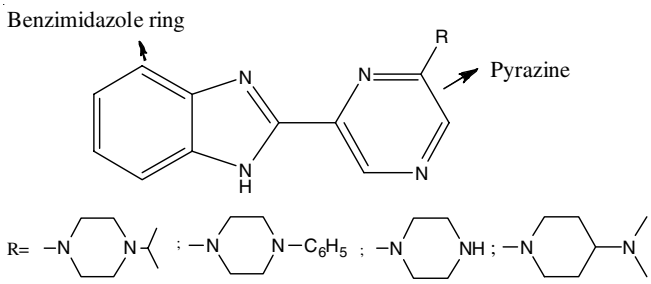


Fig. 23. Structure of pyrazine benzimidazole-piperazine/pyrazine conjugates

Berberine has several therapeutic benefits including hyperglycemic, anticancer and antioxidant activities. To further enhance the antioxidant properties of this isoquinoline based alkaloid, piperazine was conjugated in the form of Mannich base on the C-12 position of berberine (Fig. 24). A significant contribution of piperazine was observed with improved antioxidant activity of the synthesized compounds. Few analogs showed significant Fe^{3+} reducing power in FRAP assay. The compounds showed dual effect *i.e.* antioxidant and anticancer activities. All the compounds showed better activity than parent berberine. The compound with 4-methyl substitution (IC_{50}, 2.22 ± 0.26) showed potent activity when compared to the standard (IC_{50}, 2.140 ± 0.78). While in DPPH and ABTS assays, compound bearing 4-fluoro substitution showed the highest activity with IC_{50} values 12.17 ± 1.45 and 4.644 ± 0.02 µg/mL than berberine (IC_{50}, 33.16 ± 1.60 and 86.29 ± 2.11 µg/mL) and ascorbic acid (10.75 ± 0.66 and 4.76 ± 0.05 µg/mL) in respective assays [48].

Prior to this research work, berberine-based piperazine analogs (Fig. 25) were screened for their anticancer activity against HeLa and CaSKi cervical cancer cell lines and antioxidant activity by DPPH and ABTS assays. The phenyl ring was substituted with different electron releasing and electron withdrawing groups. Many of the derivatives showed promising activity [49].

When *N*-methylpiperazine or morpholine ring was coupled to 2-substituted aryl 1*H*-benzimidazole nucleus (Fig. 26), potent α-glucosidase enzyme inhibitors were obtained, which showed better activity than standard acarbose [50]. When tested for

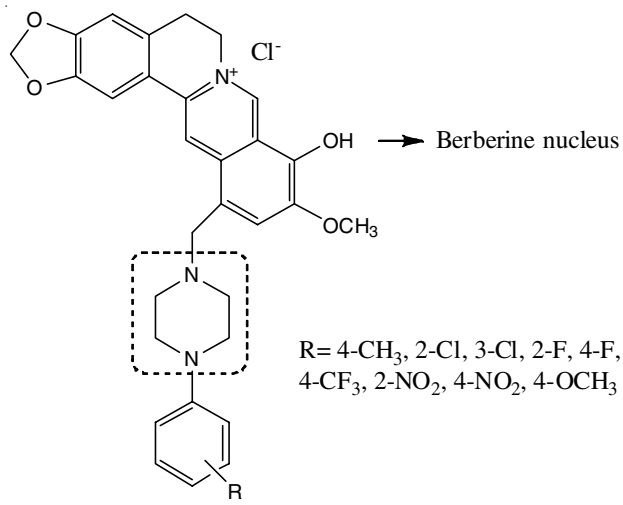


Fig. 24. Structure of piperazines linked to berberine

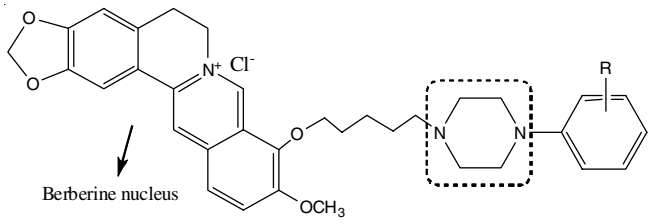


Fig. 25. Structure of piperazines linked to berberine

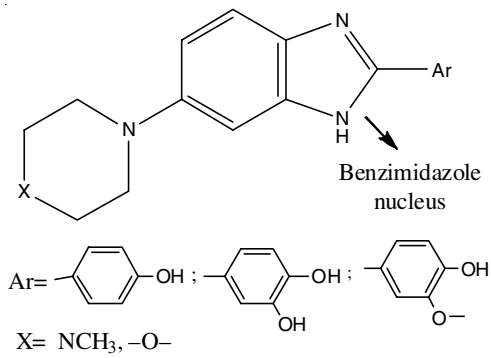


Fig. 26. Structure of piperazines linked to benzimidazole ring

antioxidant activities including cupric reducing antioxidant capacity (CUPRAC), FRAP, ABTS and DPPH methods, the hydroxyl derivatives showed potent antioxidant activity.

Sarsasapogenin is well known steroidal saponin, a multi-targeted ligand in Alzheimer's disease. Given its therapeutic profile and to further improve its activity novel 3-piperazinyl carboxylate sarsasapogenin derivatives (Fig. 27) were designed and synthesized [51]. Anti-Alzheimer's, anti-inflammatory and antioxidant activities were evaluated. Amongst all, *N*-sulfonyl piperazine carbamate derivatives exhibited better antioxidant activity compared to other derivatives. Presence of hydroxyl group improved the pharmacological effects while 4-hydroxy-3-methoxy benzyl piperazine showed a noticeable antioxidant activity [52].

Kladna *et al.* [53] reported the synthesis of flavone linked piperazines, where flavones act as antioxidant agents by inhibiting

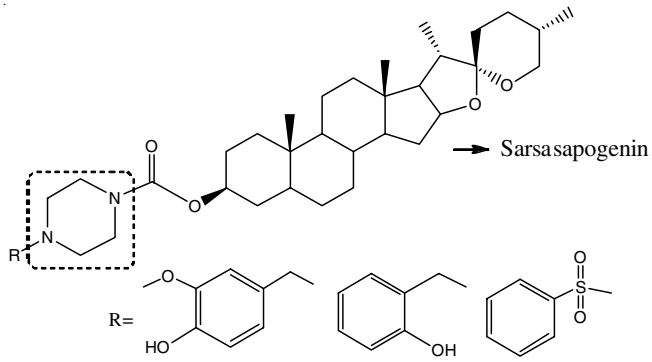


Fig. 27. Structure of piperazines linked to sarsasapogenin

lipid peroxidation. To improve the antioxidant profile of this prototype compound, this flavone moiety was linked to benzothiazole or 2-hydroxy phenyl pyrimidines nucleus *via* piperazine (Fig. 28) as a linker. Compounds incorporating the benzothiazole group on the piperazine ring showed potent antioxidant activity [53].

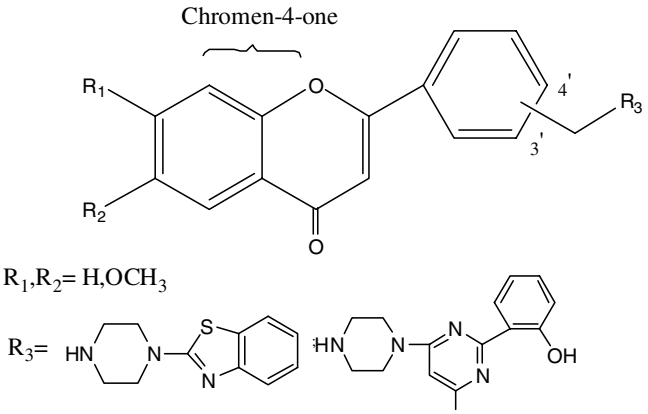


Fig. 28. Structure of piperazines linked to chromen-4-one ring

Patel *et al*. [54] evaluated anticancer and antioxidant activities of 5-hydroxy-2-phenyl-4*H*-chromen-4-one linked piperazine derivatives (Fig. 29) using cervical and ovarian cancer cell lines and DPPH and ABTS bioassays, respectively. SAR revealed that the nature and position of electron-withdrawing and donating functional groups on piperazine core can alter the antioxidant and anticancer action. Compounds with 4-CF_3; 4-Cl; 4-OCF_3; 4-OCH_3 and naphthalene substituted compounds showed more potent antioxidant activity. The compound with

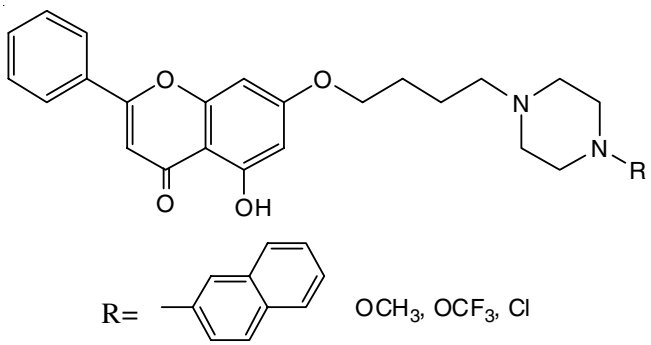


Fig. 29. Structure of piperazines linked to chromen-4-one ring

naphthalene-2-yl piperazine showed good activity with IC_{50} value 20.30 ± 0.476 µg/mL in DPPH assay using ascorbic acid (IC_{50}, 12.72 ± 0.274 µg/mL) as reference. While in the ABTS method, 4-methoxy phenyl substituted piperazine showed significant activity with IC_{50} value 5.56 ± 0.025 µg/mL when compared to ascorbic acid (5.09 ± 0.209 µg/mL) [54].

Piperazine-azole hybrids (Fig. 30) were synthesized and screened for their antioxidant, antimicrobial and enzyme inhibition activities. The antioxidant capacity was measured by DPPH, FRAP and CUPRAC assays. The fluroqinolone piperazine azole derivative bearing cyclopropyl group showed potent activity in DPPH and CUPRAC methods, respectively [55].

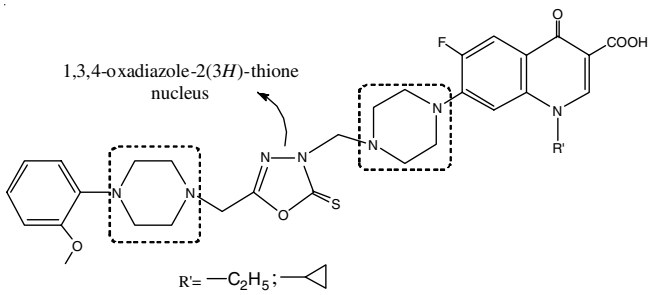


Fig. 30. Piperazine derivatives containing azole hybrids

LQFM 180, chemically 1-(4-(3,5-di-*ter*-butyl-4-hydroxy benzyl)piperazin-1-yl)-2-methoxyethan-1-one (Fig. 31) was synthesized and evaluated for antioxidant, anxiolytic and antidepressant like activity. LQFM 180 exerted potent antioxidant activity in DPPH assay with an IC_{50} value of 718.7 µmol/mL using standard compound BHT with an IC_{50} value of 104.3 µmol/mL. The anxiolytic like activity was found to be dependent on the serotonergic pathway and involved 5-HT1A receptors [56].

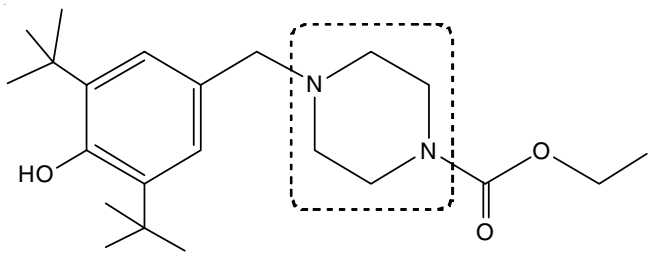


Fig. 31. Structure of LQFM 180

Novel sulphonyl piperazines linked (1,3)dioxolo(4,5)-chromenones (Fig. 32) were synthesized and tested for antioxidant activity against DPPH, ABTS and antiproliferative activity towards selected human cancer cell lines [57]. Methoxy and trifluoromethoxy analogs proved as the most favourable groups for the antioxidant activity. All derivatives with dihalo groups acted as better DPPH radical scavengers, DPPH antioxidant assay revealed that chalcone hybrids were more potent in scavenging DPPH% than phenyl derivatives. The compound bearing 2,4-di-OCH_3 chalcone hybrid with IC_{50} values 8.21 ± 0.83 and 4.82 ± 0.77 µg/mL showed highest activity than standard ascorbic acid (IC_{50}, 12.72 ± 0.27 and 5.09 ± 0.20 µg/ML) in DPPH and ABTS assays, respectively [57].

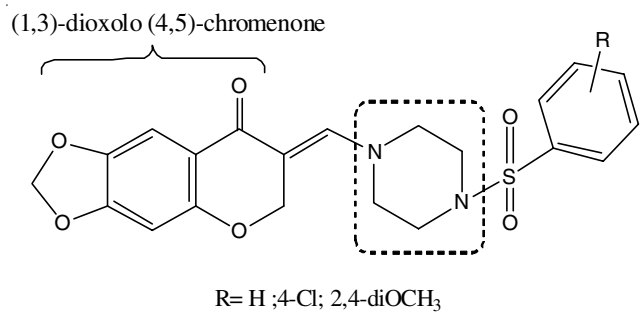


Fig. 32. Structure of piperazine linked (1,3) dioxolo(4,5)chromenone

With a similar designing approach, Bhati *et al*. [58], synthesized 1,3,4-oxadiazole incorporating piperazine derivatives (Fig. 33) and evaluated for antitubercular, antimicrobial and antioxidant activities. The antioxidant profile in the DPPH assay revealed that phenyl group substitution was favorable for radical scavenging activity. The compound bearing C_6H_5 or 4-ClC_6H_4 showed better activity with IC_{50} values 36.76 and 52.42 µg/mL compared to standard drug ascorbic acid, which showed IC_{50} value of 62.91 µg/mL [58].

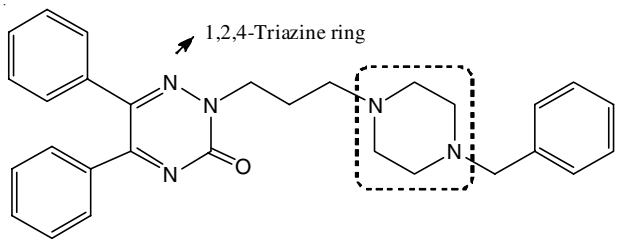


Fig. 34. Structure of piperazine linked to biphenyl-3-oxo-1,2,4-triazine ring

When biphenyl-3-oxo-1,2,4-triazine and substituted piperazines were linked (Fig. 34) potent acetylcholinesterase inhibition was observed by Tripathi *et al*. [59]. As oxidative stress is a critical factor for neurodegenerative disorders, the synthesized compounds were also evaluated for antioxidant activity and results were promising with benzylpiperazine derivative [59].

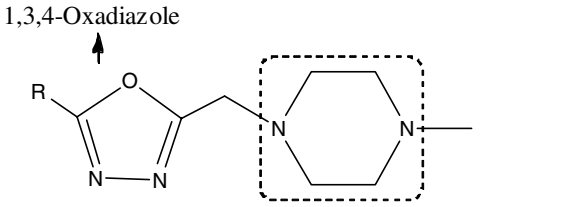


Fig. 33. Structure of piperazines linked to 1,3,4-oxadiazole

Piperazine nucleus has been introduced as a bridge in pseudo-peptidic urea or thiourea backbone and peptides having derived from phenylalanine and tryptophan showed promising antioxidant activity in DPPH, ABTS and DMPD methods [60].

By coupling 3,5-ditertiary butyl-4-hydroxy-phenyl ring with *N*-phenyl piperazine three compounds were synthesized and evaluated as antioxidants. Among the synthesized compounds, the phenyl piperazine derivative (Fig. 35) showed potent antioxidant activity in comparison to the references used BHT [61].

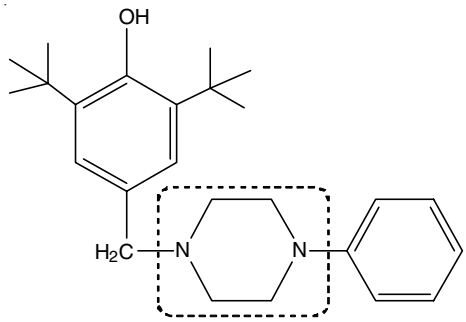


Fig. 35. Structure of piperazine with 3,5-ditertiary butyl-4-hydroxy-phenyl ring

Novel series of indole heterocycles incorporating various substitutions (Fig. 36) were synthesized and evaluated for antioxidant activity by DPPH method. The piperazine substituted compound showed medium antioxidant activity in comparison with standard vitamin C [62].

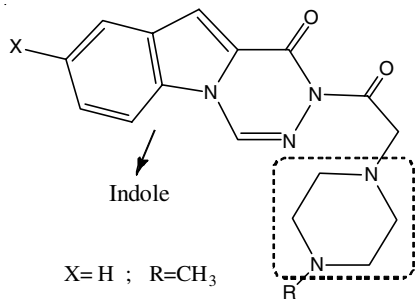


Fig. 36. Structure of piperazine linked to indole ring

Antioxidant, analgesic and anticonvulsant activities were summarized for compounds possessing dihydrofuranone linked to the piperazine ring system (Fig. 37). The antioxidant activity was measured by ABTS radical scavenging method and expressed in terms of Trolox equivalent antioxidant capacity (TEAC) and IC_{50} values. The derivatives showed excellent antioxidant activity with IC_{50} value 12.35 ± 0.75 mM [63]. In the subsequent study, trifluoromethyl containing derivative showed significant activity in FRAP, SOD but did not affect CAT activity [64].

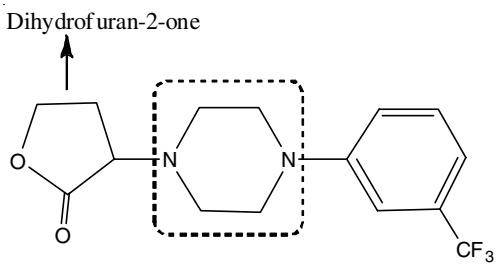
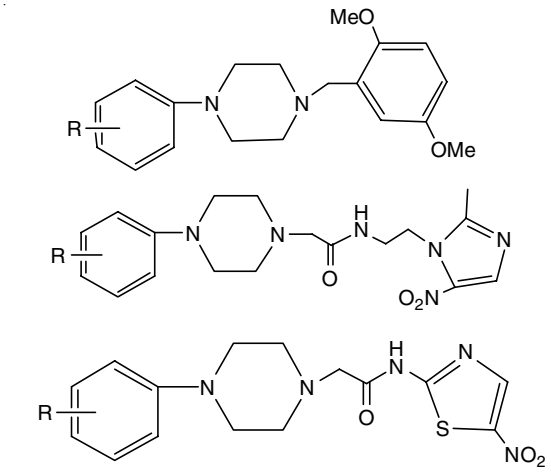


Fig. 37. Structure of piperazines linked to dihydrofuran-2-one ring

Taking aryl piperazine as a core structure, a range of derivatives was synthesized linking it with the substituted aryl and heteroaryl rings (Fig. 38). The activity profile was demonstrated on enzymes like mono amine oxidase, cholinesterase,

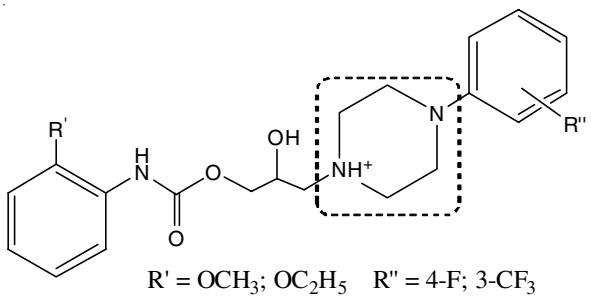


R = H, 4-Me, 4-OMe, 4-NO_2, 4-CF_3, 4-Cl, 4-F, 3-F, 2-F

Fig. 38. Structure of piperazine derivatives containing substituted aryl and heteroaryl rings

and GPCRs. All the compounds exhibited significant antioxidant activity compared to ferulic acid as a standard [65].

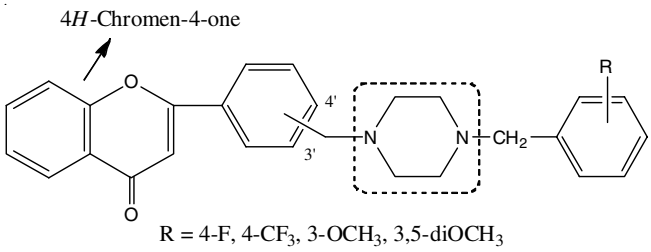
In another study by Malik *et al*. [66], aryl piperazine unit was attached to substituted 2-alkoxyphenylcarbamic acid and the derivatives (Fig. 39) were evaluated for antioxidant activity by ABTS and FRAP assays. Methoxy and 4-fluoro derivatives showed promising activity with 35.22 ± 1.03 % ABTS. While in FRAP method, ethoxy and 4-fluoro substituted derivative showed the highest activity with ascorbic acid equivalent value 3.02 ± 0.07 mg/mL when compared to reference drugs atenolol and carvedilol [66].



R' = OCH_3; OC_2H_5 R'' = 4-F; 3-CF_3

Fig. 39. Structure of piperazine attached to substituted 2-alkoxyphenylcarbamic acid

Novel piperazinyl flavone derivatives (Fig. 40) containing phenyl ring with different substituents were synthesized by Berczynski *et al*. [67] and *in vitro* antioxidant activity against superoxide anion radical, hydroxyl radical, DPPH radical, and hydrogen peroxide scavenging was screened. The total antioxidant status based on the absorbance of $ABTS^{\bullet}$ and total antioxidant capacity using the Fe(III)-ferrozine complex were also monitored. Synthesized analogs also showed remarkable antioxidant activity. The best antiradical activity was found for the compound with methoxy groups on the phenyl ring whereas the presence of methoxy or trifluoromethyl groups resulted in higher $ABTS^{+\bullet}$ and ion Fe(III) reduction. The activity was compared with the standards of ascorbic acid and tocopherol [67].



R = 4-F, 4-CF_3, 3-OCH_3, 3,5-diOCH_3

Fig. 40. Structure of piperazinyl flavone derivatives

In year 2020, the same research team reported eight new flavone derivatives in which piperazine ring was substituted with various substituted phenyl rings (Fig. 41) and their antioxidant activities in superoxide anion radical, hydroxyl radical, DPPH, ABTS and FRAP assays. Best antioxidant activity was found for the piperazinyl analog containing 2,5-dimethoxy phenyl derivative [68].

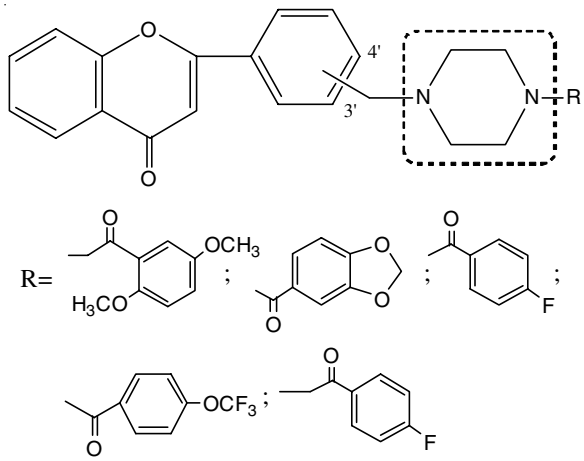
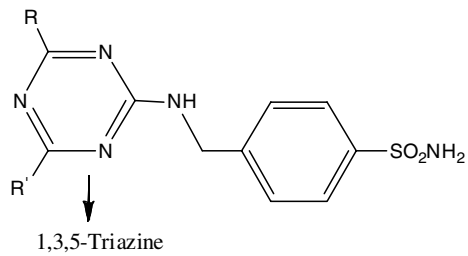


Fig. 41. Structure of piperazinyl flavone derivatives

Recently, 1,3,5-triazine analog bearing piperazine (Fig. 42) was synthesized by Havrankova *et al*. [69]. To study the antioxidant abilities, 1,3,5-triazine derivatives were also synthesized using amino alcohol/phenol, chalcone or stilbene. The activity was determined by the ABTS method in terms of EC_{50} and % inhibition. The piperazine substituted derivative showed excellent radical scavenging activity in comparison with standards ascorbic acid and Trolox [69].



R = $[N(CH_2CH_2)_2N]COOCH_3$; $[N(CH_2CH_2)_2N]CH_2COOCH_3$; $[N(CH_2CH_2)_2N]CH_2CH_2COOCH_3$

R' = $NH\text{-}CH_2CH(OH)CH_2OH$; $NH\text{-}CH_2CH_2\text{-}C_6H_4(1,4)\text{-}4\text{-}SO_2NH_2$; $NH\text{-}C_6H_4(1,4)\text{-}4\text{-}OH$

Fig. 42. Structure of piperazine linked to 1,3,5-triazine ring

A novel series of piperazine and amide linked dimeric 1,2,3-triazoles (Fig. 43) were synthesized and evaluated for antioxidant, antifungal and antitubercular activities. The compound bearing 3-chloro or 4-methyl substituted benzamine showed antioxidant activity with IC_{50} values 10.12 ± 0.25, 10.64 ± 0.29 µg/mL, when compared to standard BHT having IC_{50} value 16.47 ± 0.18 µg/mL [70].

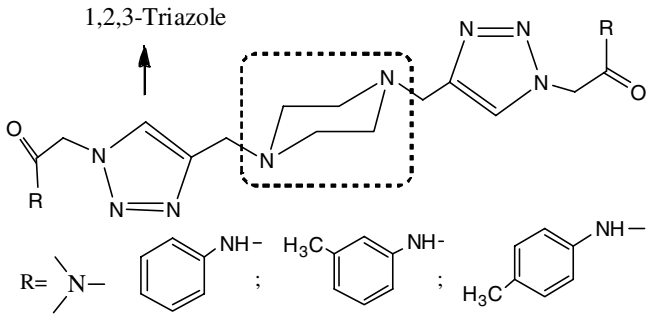


Fig. 43. Structure of piperazine linked to 1,2,3-triazole ring

Promising antioxidant activity was reported for piperazine substituted derivative where quinoline-8-ol and 4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-amine were substituted on *N*-atoms of piperazine ring (Fig. 44). The compound was also screened for dopamine agonistic activities and neuroprotective properties. The derivative showed significant activity in DPPH assay when compared with ascorbic acid as a standard [71].

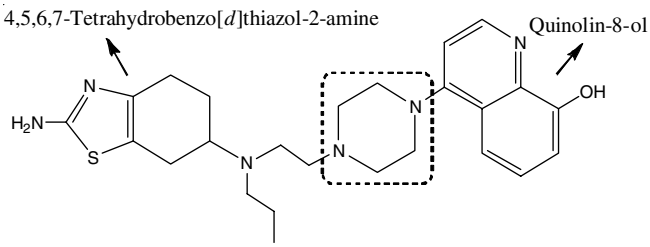


Fig. 44. Structure of piperazine derivative containing quinoline-8-ol and 4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-amine group

N-substituted-2-amino-1,3,4-thiadiazoles (Fig. 45) were synthesized and screened for antioxidant and antitumor activities [72]. Antioxidant activity was evaluated by the ABTS method and the substituted compound showed moderate antioxidant activity with % inhibition of 25.7, when compared to standard ascorbic acid with 88.57% inhibition [72].

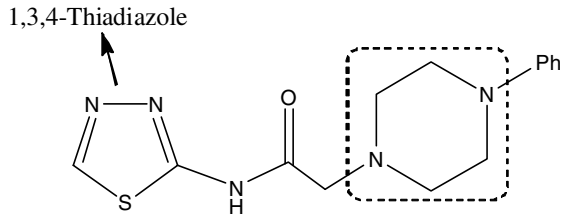


Fig. 45. Structure of piperazine linked to 1,3,4-thiadiazole ring

Zargar *et al*. [73] studied the anti-inflammatory and antioxidant potential of aripiprazole (ARI) (Fig. 46) alone and in combination with grapefruit juice in hydrogen peroxide induced

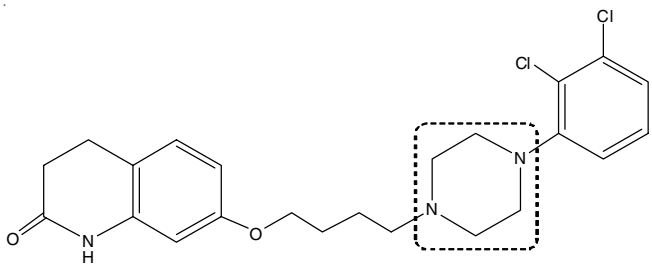


Fig. 46. Chemical structure of aripiprazole

oxidative stress in mice. Results indicated synergistic effects in the studied model. The good antioxidant activity and the synergistic effects were attributed to the inherent antioxidant and anti-inflammatory activity of grapefruit juice [73].

A series of new conazole analogs derived from 1-(4-fluorophenyl)piperazine (Fig. 47) were synthesized and antioxidant, antiurease and antimicrobial activities were demonstrated. Antioxidant capacity was demonstrated against DPPH, FRAP and CUPRAC methods in terms of µmol TE/g. Most of them showed good activity [74].

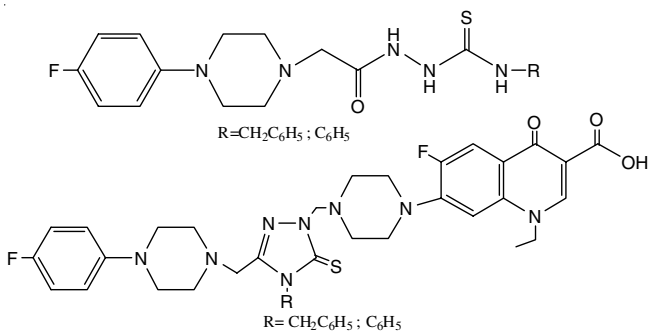


Fig. 47. Structure of new conazole analogs derived from 1-(4-fluoro-phenyl)-piperazine

Mn(II) complexes containing bridging piperazinedithiocarbamate (pipdtc) and various amino acids such as glycine, alanine, phenylalanine, tyrosine, methionine and cysteine were synthesized and evaluated for antimicrobial, anticancer against cancer cell line MCF-7 and antioxidant activities. Good antioxidant activity was observed in DPPH and FRAPS assays. Phenylalanine (70.2 & 270.1%) and alanine (63.3 & 259.8%) complexes exhibited better antioxidant capacity when compared with BHT as a standard (99.9 & 299%) in respective assays [75]. Similar to this work, piperazinedithiocarbamate bridged homo binuclear mixed Co(II) complexes were synthesized with amino acids such as alanine, phenylalanine, glycine, methionine, tyrosine and screened for antioxidant, anticancer, antibacterial and antifungal activities. The tyrosine complex showed good antioxidant activity with 58.7% and 228.7 in comparison to standard BHT in DPPH and FRAP methods, respectively [76].

Two macrocyclic Schiff base complexes (Fig. 48) were synthesized and screened for antioxidant activity against DPPH assay and anticancer activity against human gastric and lung cell lines. All the complexes showed good antioxidant activity with IC_{50} values 0.19 mg/mL (Mn, Pt) and 0.18 mg/mL (Zn) in comparison with the standards ascorbic acid (0.14 mg/mL) and quercetin (0.13 mg/mL) in DPPH assay [77].

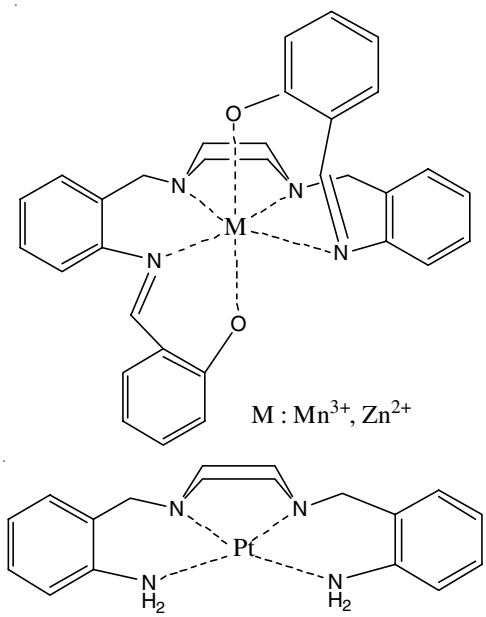


Fig. 48. Chemical structures of piperazine metal complexes

Several heterocyclic rings were also explored for a variety of biological effects including antioxidant activity [78]. The piperazine ring is one of the several interesting heterocyclic rings with the antioxidant potential.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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