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Antioxidant and Metal chelating Activities of Some Novel Phenothiazine incorporated Tetrazole Heterocycles

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ABSTRACT

*A series of 10-substituted-2-(1H-tetrazol-5-yl)-10H-phenothiazines **(3a-f)** with good free radical scavenging activity (RAS) were synthesised. The compounds **3a**, **3b** and **3c** showed better (RAS) than the compounds **3d, 3e, 3f**. To prove whether these 10-substituted-2-(1H-tetrazol-5-yl)-10H-phenothiazines compounds may exert their antioxidant effect through transition metal ion chelation, the ferrous chelating abilities of these were investigated. The above results indicated that the transition metal ion chelation play an important role in their antioxidant.abilities.*

Keywords: Phenothiazine, Tetrazole, Antioxidant activity, Metal chelating activity.

INTRODUCTION

Phenothiazine and its derivatives have been under investigation for a long time because of their broad spectrum of biological activities, which include antibacterial[1], antifungal[2], antitubercular[3], schizophrenic[4,5], and anti-inflammatory[6]. The 10-substituted-10*H*-phenothiazine with ribofuranosides has been shown to possess antioxidant activity. Hence, in the present study the second position of phenothiazine was used as target for chemical modification by incorporation of tetrazole.

In the present paper, we designed 10-substituted-10*H*-phenothiazines and 10 substituted-2-(1*H*-tetrazol-5-yl)-10*H*-phenothiazines (fig 1) and antioxidant activity of all the derivatives were evaluated, especially with regards to their transition metal ion chelation activity .

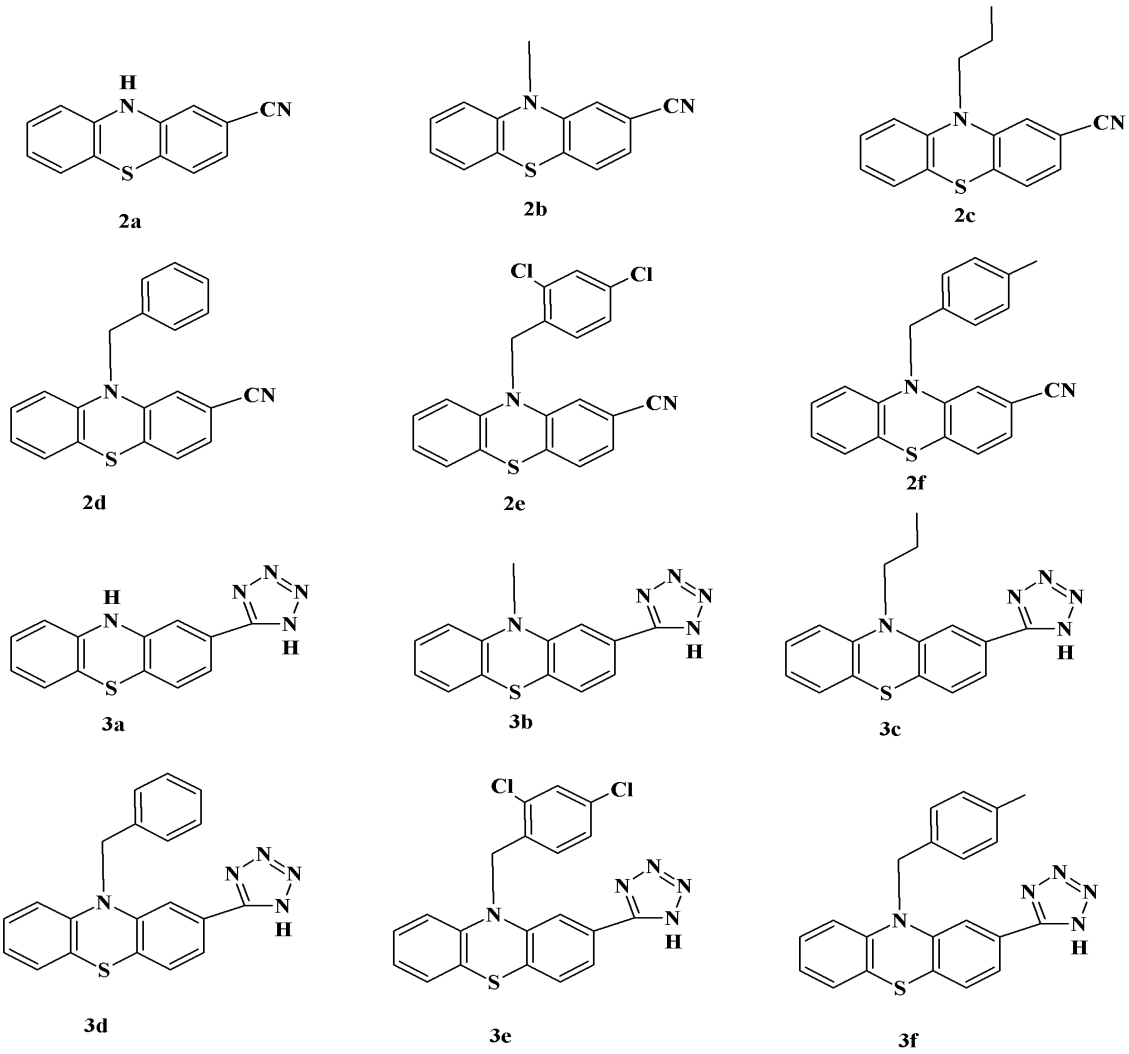

Fig. 1 Structure of the phenothiazine derivatives

MATERIALS AND METHODS

2,6-Diter-butyl-4-methylphenol (BHT), 1,1-diphenyl-2-picrylhydrazyl (DPPH•) were purchased from Sigma Chemicals Co. (St. Louis, MO, USA). All chemicals and solvents used were of analytical grade. For the in vitro tests, a Shimadzu UV–Vis double beam spectrophotometer was used.

Antioxidant activities : Free radical scavenging activity of the synthesized compounds **2a-f** and **3a-f** were carried based on Brand-Williams et al [7] the scavenging activity of stable DPPH. 100 mg mL^{-1} of each test sample and the standard BHT was taken in different test tubes and the volume was adjusted to 1 mL using MeOH. Freshly prepared 3 mL of 0.1 mM DPPH solution was mixed and vortexed thoroughly and left in dark for 30 min. The absorbance of stable DPPH was measured at 517 nm. The DPPH control (containing no sample) was prepared using the same procedure. Radical scavenging activity was expressed as the inhibition percentage and was calculated using the equation of DPPH radical.

DPPH radical scavenging activity (%)

= [(Abs Control - Abs Sample) /Abs Control] x 100:

Where Abs Control is the absorbance of DPPH radical + methanol; Abs Sample is the absorbance of DPPH radical + test sample/standard BHT

Iron-chelating ability : The chelating effect was determined according to the literature method [8]. The test solution 100 mg mL^{-1} of each test sample in methanol was added to a solution of 2 mM $FeCl_2$ (0.05 mL) and the reaction was initiated by adding 5 mM ferrozine (0.2 mL) and total volume was adjusted to 5 mL with methanol. Then, the mixture was shaken vigorously and left at room temperature for 10 min. The absorbance of the solution was measured spectrophotometrically at 562 nm. The inhibition percentage of ferrozine–Fe+2 complex formations was calculated by the formula:

Metal chelating effect (%) = $[(A_{control} - A_{sample}) / A_{control}] \times 100$

where $A_{control}$ is the absorbance of control (control contains $FeCl_2$ ferrozine complex) and A_{sample} is the absorbance of test compounds. Ascorbic acid is used as control.

RESULTS AND DISCUSSION

All the synthesized compounds **2a-f** and **3a-f** were evaluated for their antioxidant and metal chelating activities.

Antioxidant Activity: Free radical scavenging activity by DPPH method. All compounds have exhibited free radical scavenging capacity.by comparison with the standard Butylated Hydroxytoulene (BHT). DPPH assay were carried out for compounds **2a-f** and **3a-f** at 100 µM concentration. Among the tested compounds **2a-f** and **3a-f**, compounds **3a, 3b, 3c** showed significant amount of DPPH activity (>70%). The other derivatives were not significant compared to the standard BHT. The variation in DPPH scavenging capacity could be attributed to formation of tetrazole ring and electron donating group at 10 substituted-2-(1*H*-tetrazol-5-yl)-10*H*-phenothiazine. The results are tabulated in (Table 1).

Table-1. DPPH radical scavenging activity of compounds 2a-f and 3a-f

Compound No.	DPPH assay in %	Compound No.	DPPH assay in %
2a	18.1	**3a**	72.9
2b	23.8	**3b**	74.4
2c	15.7	**3c**	79.2
2d	13.7	**3d**	55.4
2e	12.7	**3e**	52.7
2f	11.2	**3f**	57.1
BHT	92.13	BHT	92.13

Metal-chelating Activity: Iron chelating activity is a capacity to measure the antioxidant activity Iron binding capacity of the synthesized compounds and the reference compound EDTA were examined (Table 2). The range and mean of Fe^{+2} chelating capacities varied significantly among the different compounds on the basis of substitution at 10 substituted-2-(1*H*-tetrazol-5-yl)-10*H*-phenothiazine. The compounds **3a**, **3b** and **3c** showed good chelating ability (60.3, 60.4 and 55.6%, respectively). Though compounds **3a**, **3b,** and **3c** showed relatively high free radical scavenging activity, they had lower ferrous ion chelating capability compared with the standard EDTA. The compounds **3d, 3e,** and **3f** showed satisfactory activity compared with the standard. On the other hand, the activity seems to increase with the presence of electron donating substituents at 10 substituted-2-(1*H*-tetrazol-5-yl)-10*H*-phenothiazines.

Table-2 Iron chelating activity of compounds 2a-f and 3a-f

Compound No.	Iron chelating activity assay in %	Compound No.	Iron chelating activity assay in %
2a	10.3	**3a**	60.3
2b	18.6	**3b**	60.4
2c	10.4	**3c**	55.6
2d	10.05	**3d**	33.5
2e	11.00	**3e**	30.7
2f	11.15	**3f**	35.8
EDTA	83.6	EDTA	83.6

APPLICATIONS

10-substituted-10*H*-phenothiazines and 10 substituted-2-(1*H*-tetrazol-5-yl)-10*H*-phenothiazines have antioxidant activity and transition metal ion chelation activity.

CONCLUSIONS

In conclusion, we have shown that the Tetrazole derivatives have good radical scavenging activity chelation with transition metal ions. The results indicated that the Tetrazole derivatives may exert their antioxidant effect through transition metal ion chelation and the transition metal ion chelation play an important role in their antioxidant activity.

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