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Antioxidant Potential Study of some Synthesized N-Containing Benzothiazine Derivatives

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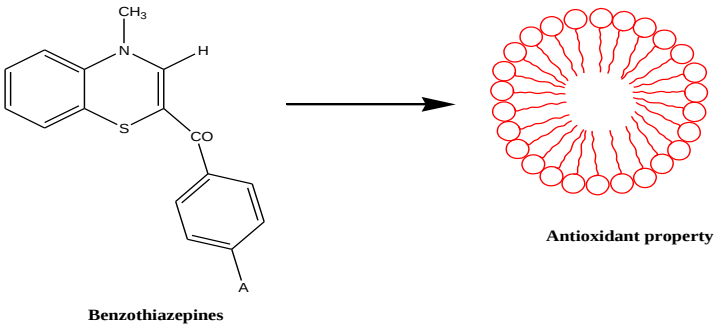
ABSTRACT

Heterocycles having heteroatom N, S shows profound biological activities like antibacterial, antimicrobial, antihypertensive, anticancer etc. in addition to above said activities, a new series of synthesised compounds, 1,4-benzothiazine derivatives were found to show good antioxidant activity. To find the valuable bioactivity of above said ring transformed compounds, series of 4H-1,4-benzothiazine derivatives were synthesized through C-2 ring expansion of substituted 1,3-benzothiazoles. The antioxidant activities of all the synthesised compounds were screened by 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) method having ascorbic acid as a standard. The synthesized compounds shows moderate to good antioxidant activity.

Graphical abstract



Benzothiazepines

Keywords: 1,4-Benzothiazines, DPPH, Ascorbic acid, Antioxidant property, Free radicals

INTRODUCTION

Heterocycles with N, S heteroatom especially 4H-1,4-benzothiazine and their derivatives are of immense importance as they are known to show numerous biological activities like antibiotic, anticancer, antiviral, antifungal, antimicrobial and antiparkinson, anti-inflammatory, antihypertensive, antitumor, antialdosoreductase, antirheumatic, antiarrhythmic, anti-HIV antiallergic etc., [1-11]. In view to above biological activities, due to presence of N-C-S linkage in them, there are useful synthetic templates for medicinal and therapeutic industry [12]. Owing to this, eminent research is going on to synthesize such multifarious active compounds [8,9-13]. A variety of natural substances are there in our nature which have good antioxidant potential like fruits having vitamin C, some vegetables, red wine and there are also some plants which exhibit antioxidant potential [14-16]. The activity can be illustrated as power of these antioxidants to scavenge the free radical which oxidatively damages lipids, proteins and nucleic acids in our body. Due to the chemical structure of antioxidant enriched vitamin C having C=O group and having N-H radicals have inspired us to synthesize 4H-1,4-benzothiazine derivatives and to screen them for their antioxidant activities. Firstly, new series of 4H-1,4-benzothiazines have been synthesised by C-2 ring expansion of alkylated 1,3-benzothiazole derivation through green protocol [17] viz. Ultrasonication. In the present study, we screen these synthesised compounds for their antioxidant potential by DPPH radical scavenging activity.

MATERIALS AND METHODS

The chemical structure of the synthesised compounds have been shown in Figure 1.

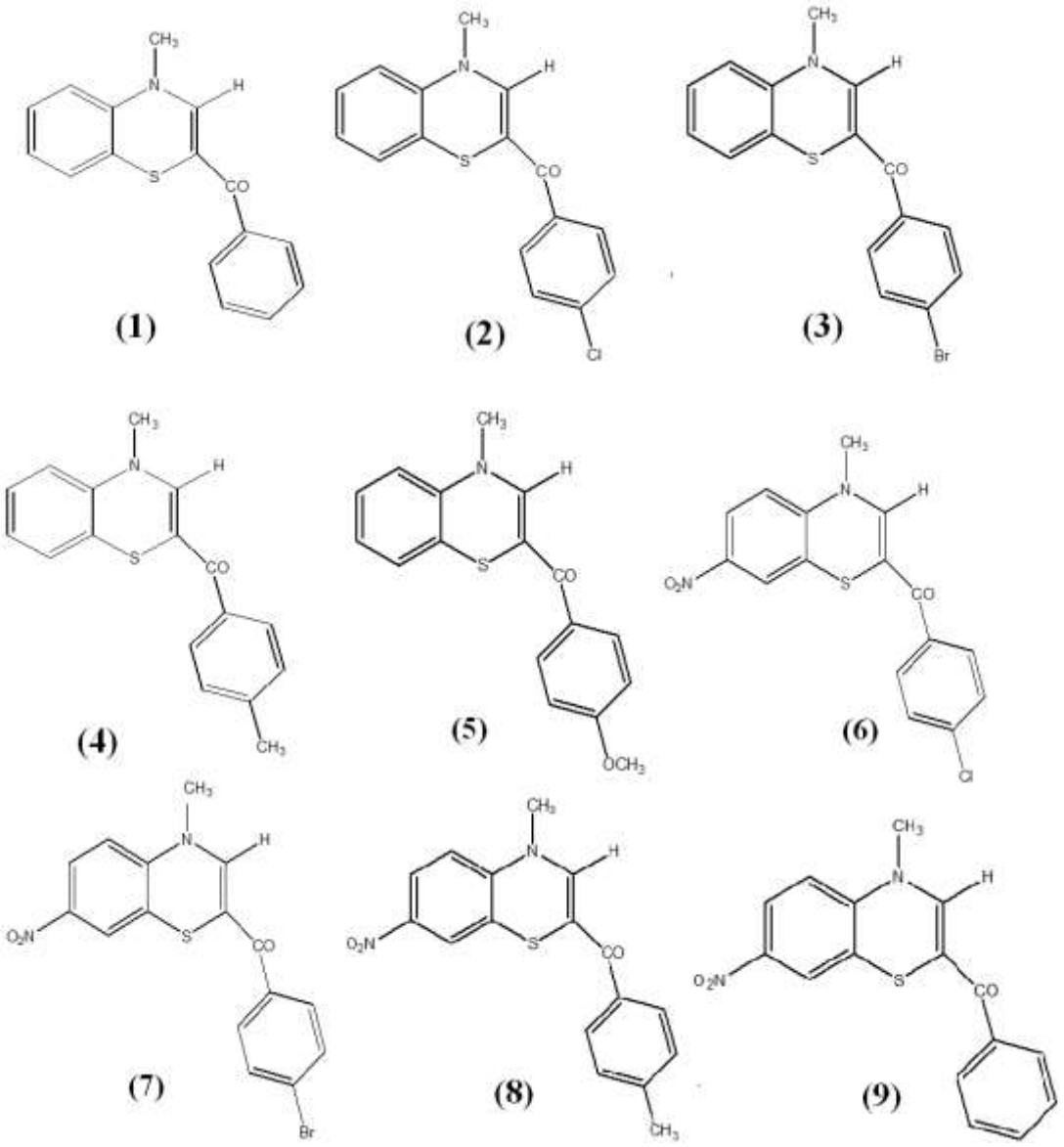


Figure 1: Chemical structure of synthesised compounds (1-9)

As per the mechanism reported in the literature, autoxidation of unsaturated lipids is due to the presence of free radicals [18,19]. The antioxidant potential of an synthesised compounds can be calculated by using 1,1-Diphenyl-2-Picrylhydrazyl (DPPH) radical scavenging activity [20-22]. The notable features of antioxidants were that they donate hydrogens from phenolic hydroxy groups and also interfere in the oxidation process of free radical chain present in the lipids. As the structure of DPPH depicts that it contains stable free radicals along with odd number of electrons which proves to be useful for determining antioxidant properties of different compounds. The synthesized compounds show antioxidant activity when screened against DPPH scavenging activity. The activity was performed with the help of method given by Yalcin nas Cavusoglu with little bit modifications [23]. Free radical DPPH was used as reagent and ascorbic acid in these experiments. Aliquots of different concentration viz. 100 µl (1-20 mg/ml) of the compounds or standard ascorbic acid in methanol were taken. Then, absorbance was recorded at 517 nm against blanck. The percentage inhibition was calculated by using following Equation:

$$\% \text{ [DPPH radical]} = [(Ac\text{-}As/Ac)] \times 100$$

Where, As=Absorbance of the sample and Ac=Absorbance of the control.

Five different test tubes were marked with aliquots of different concentrations (1, 5, 10, 15 and 20 mg/ml). The synthesised compounds and ascorbic acid concentration were prepared in triplicates to minimize the error in the readings. The required amount of DPPH was dissolved in methanol to make it 0.004% (weight/volume) ratio. Shaker or magnetic stirrers were used to prepare the homogenous mixture of synthesised compound solutions. In each test tube, 3 ml of DPPH solution was added with the help of pipette to maintain accuracy. After the addition, all the samples including blanck were incubated at room temperature in dark for 30 min. For the blanck, equal amount i.e., 3 ml of DPPH was added in pure methanol to prepare solution. The readings for inhibition were taken in triplicates and the average absorbance was used for further calculation. Ascorbic acid was used as a standard. The antioxidant potential of all the synthesised compounds was there in Table 1.

Table 1: Antioxidant potential of synthezised compounds

Test samples	Percentage (%) radical scavenging activity				
	1 mg/ml	5 mg/ml	10 mg/ml	15 mg/ml	20 mg/ml
1	20.01	39.01	56.01	69.01	79.01
2	25.22	45.33%	58.66%	72.03	85.22%
3	26.99	48.99	59.87	76.66	87.09
4	18.09	30.76	50.44	61.54	73.23
5	17.78	31.09	53.23	62.75	72.98
6	17.33	25.23	33.23	50.66	62.12
7	18.07	29.22	37.05	59.43	71.95
8	19.03	30.32	40.42	62.56	72.22
9	16.33	29.88	34.23	49.87	66.23
Ascorbic acid	58.42%	-	-	-	-

Mechanism of free radical scavenging activity

The method which was used extensively for the evaluation of antioxidant potential was DPPH free radical scavenging activity. To measure the antiradical power by the above said method is quite feasible. Due to presence of odd electrons in DPPH free radical, the blanck will show the absorbance at 517 nm. As, we add the different synthesised compounds with concentration mg/ml into the 3 ml DPPH solution. After incubation, the colour of the solution decolorizes from dark purple to light colour viz. Yellow sometimes or light purple. This decolourization is due to number of captured unpaired electrons from the synthesized compound added. When odd electrons of DPPH get paired with hydrogen radical obtained from synthesized compounds, a stable reduced DPPH-H was formed which affect the colour of DPPH solution. When absorbance of aliquots were recorded, the absorbance decreases from 517 nm, which implicates the disappearance of odd electrons from the solution and formation of diamagnetic spin paired molecule [24].

RESULTS AND DISCUSSION

The antioxidant potential of the synthezised compounds were summarized in Table 2. The chemical structures of the organic compounds strongly influence the bioactive behaviour of that particular compound. As a series of 4H-1,4-benzothiazines were synthesised, in these compounds due to presence of N-CH_2, it reflects that these compounds have greater tendency to show antioxidant activity. The advantageous feature of some of synthesised compounds to show maximum antioxidant activity is presence of halogen group in them. Due to –Cl and –Br group in compounds 2, 3, 6 and 7 sharply enhance the antioxidant activity. Compound 3 shows maximum efficacious antioxidant as it has strong reducing power. The compounds 6, 7, 8 and 9 shows less antioxidant activity in comparison to compounds 1, 2, 3, 4 and 5 as they contain –NO_2 group in their structure. -NO_2 group is known as deactivating group which may affect the activity. Even though, the compound 6, 7 shows moderate antioxidant activity.

The present study reveals that N, S-heterocycles are important structural motifs as they show tremendous biological activities mainly antioxidant activity. The keto groups in N-heterocycles profoundly affect the chemical and biological behaviour [25]. The synthetic pathway of these synthesised compounds was ring transformation viz. Ring expansion in basic medium through ultrasonication. The synthetic route facilitates the introduction of C=O group from alpha-haloketones which somewhat leads to their biological activities. The presence of nitrogen, sulphur heteroatom along with halogen group like –Cl, -Br greatly enhance their power to absorb free radicals. The starting material 1,3-benzothiazole were not utter to exhibit good antioxidant potential, but on the other hand the synthesised compounds have N-CH_2 accelerate their activity along with other factors like keto group, halogens etc. Our present finding reveals that heterocyclic system with substituted halogen group (Cl- or Br-) depicts significant antioxidant property. In all the synthesised compounds, it was notable that molecules having halogen (bromine/chlorine) substitution viz. 2, 3, 6 and 7 compounds were found to be more active than their unsubstituted compounds. With the loss of proton from the synthesised compounds in radical scavenging activity. The conjugation in the chemical structure may also enhance the activity. There were no evidences of this enhancement but it was just a proposed theory. Compound 2, 3 were proving to be the most efficient antioxidant. This may be due to the halogen group in them as compared to other moieties. –Cl or –Br group being highly electronegative and have lone pair of electron shows prominence effect on the formation followed by stabilization of the nitrogen-ring radical sandwiched between aromatic ring system in compounds 2, 3. Due to auxiliary stabilization, free radicals from compounds 2, 3 would have greater propensity to entrap free radical on a rapid rate than correspondingly similar compounds.

CONCLUSION

As, there are so many heterocyclic compounds having heteroatom N and S reported in the literature to have profound biological activities. In support to that we have synthesised a new series of 1,4-benzothiazine derivatives which exhibit antioxidant potential. Were to discuss the mechanism, why this type of synthesised compounds shows antioxidant potential. The substitutions on benzothiazine ring greatly influenced there antioxidant activity as, compound 2, 3 and 7 shows maximum antioxidant activity in comparison to other unsubstituted compounds.

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