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Original article

# Synthesis and antioxidant activity of quinolinobenzothiazinones

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LPO (lipid peroxidation)
Quinolino[3,4-b][1,4] benzothiazin-6(5H)-ones
MDA (malondialdehyde)

ABSTRACT

A new series of structurally diverse quinolinobenzothiazinones has been synthesized with the annulation of heterocyclic structural pharmacophores. The synthesized quinolinobenzothiazinones have been evaluated for their antioxidant (LPO & GSH) and radical scavenging activities (DPPH and ABTS assays).



## 1. Introduction

The synthesis of heterocyclic systems is of continuing interest in the field of organic chemistry because most of the compounds with biological activity are derived from heterocyclic structures. 1,4-Benzothiazines constitute an interesting class of privileged heterocycles with promising biological and therapeutically activity and have been reported as calcium channel blockers [1], $K_{ATP}$-channel openers [2], phosphodiesterase 7 inhibitors [3], 5-$HT_3$ antagonists [4], anticataract agents [5], dopamine $D_4$ [6], $Na^+/H^+$ exchange inhibitors [7], coagulation factor $X_a$ inhibitors [8] and matrix metalloproteinase inhibitors [9]. 1,4-Benzothiazines have also been reported as new antiallergic [10] and antirheumatic [11] agents. Similarly, quinolone ring system is also a privileged heterosystem and appears in several natural and synthetic compounds of significant pharmacological properties with their use as HIV protease inhibitors [12], antimalarials [13], drugs for treatment of asthma [14], broad spectrum antibacterial agents [15], etc.

The annulation or incorporation of two or more heterocyclic systems (pharmacophoric structures) has been one of the best approaches in rational drug design in generating new structurally diverse drugs (with fused heterocycles) as structural diversity is obviously directly related to the compounds potentiality endowed with pharmacological activities. The annulation of quinolone ring system with other heterosystems, such as with pyrane, results in pyranoquinolone structural scaffold and its presence in the natural products exhibits diverse biological activities such as antibacterial [16–18], antifungal and antialgal [19], anti-inflammatory [20] and antimalarial [21] as well as inhibition of calcium signaling [22], platelet aggregation [23] and nitric oxide production [24]. The alkaloids with such fused structural motif have also been reported to exhibit cancer cell growth inhibitory activity and are investigated as potential anticancer agents [25,26]. In addition, xanthosimuline with pyranoquinolone structural motif is active against multi drug resistant kB-VI cancer cells, while huajiasimuline exhibits a -selective cytotoxicity profile showing greatest activity with estrogen-positive ZR-75-I breast cancer cells [27]. Similarly benzopyranobenzothiazines incorporating benzopyrane fused with 1,4-benzothiazine have shown interesting cytoprotective effects against t-BHP-induced cytotoxicity [28].

Encouraged by the promising biological activities of the structurally diverse heterocycles with fused heterocyclic systems and our continuing research programme on the synthesis of therapeutically interesting heterocycles [29–32], we have designed and

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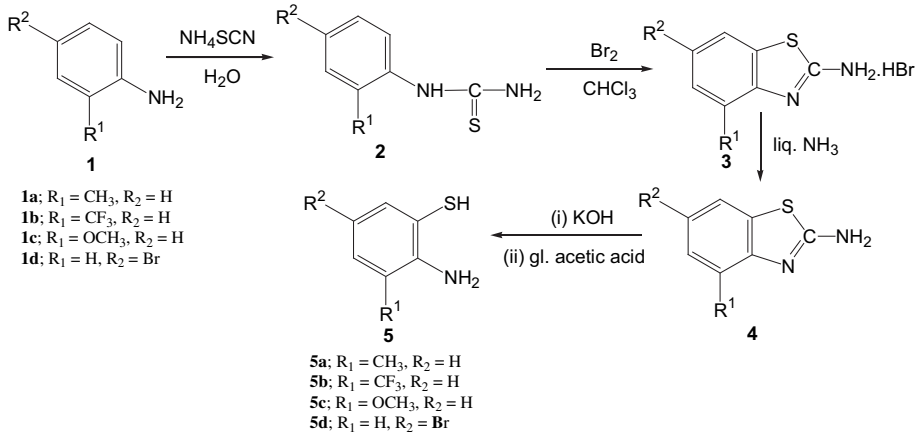



**Scheme 1.** Reaction protocol for the synthesis of 2-aminobenzenethiols.

synthesized quinolinobenzothiazinones, based on two privileged biodynamic heterocyclic scaffolds; quinolone and 1,4-benzothiazine, with an aim of developing new structural motif which will provide the multi-target drugs with promising bioactivity. The synthesized quinolinobenzothiazinones have been screened for their antioxidant activity by DPPH radical scavenging and $ABTS^{+}$ radical cation decolourization assays. The synthesized compounds have also been evaluated for their antioxidant activity in Swiss albino mice.

## 2. Chemistry

2-Aminobenzenethiols were synthesized by alkaline hydrolysis of 2-aminobenzothiazoles which, in turn, were prepared by cyclization of phenylthioureas obtained by the reaction of substituted anilines with ammonium thiocyanate (Scheme 1) [30,31].

4-Hydroxyquinolin-2-ones were synthesized by the reaction of substituted aniline with malonic ester in the presence of polyphosphoric acid (Scheme 2) [33].

Quinolino[3,4-b][1,4]benzothiazin-6(5H)-ones were synthesized in quantitative yields in a single step involving the reaction of 2-aminobenzenethiols with 4-hydroxyquinolin-2-ones in the presence of dimethyl sulphoxide. Under the reaction conditions, dimethyl sulphoxide acts as a solvent as well as oxidizing agent and the reaction proceeds regioselectively involving in situ formation of enaminoketone intermediate **8** which undergoes intramolecular cyclization with the cleavage of S–S bond (Scheme 3).

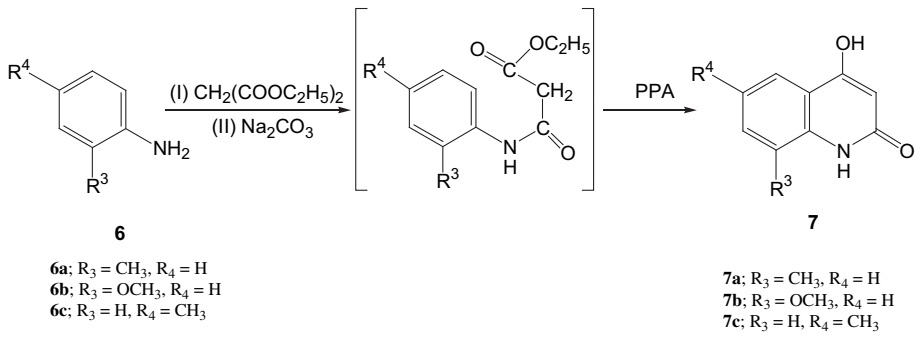
The synthesized compounds were crystallized from methanol and their structures were assigned by their analytical and spectral data.

## 3. Results and discussion

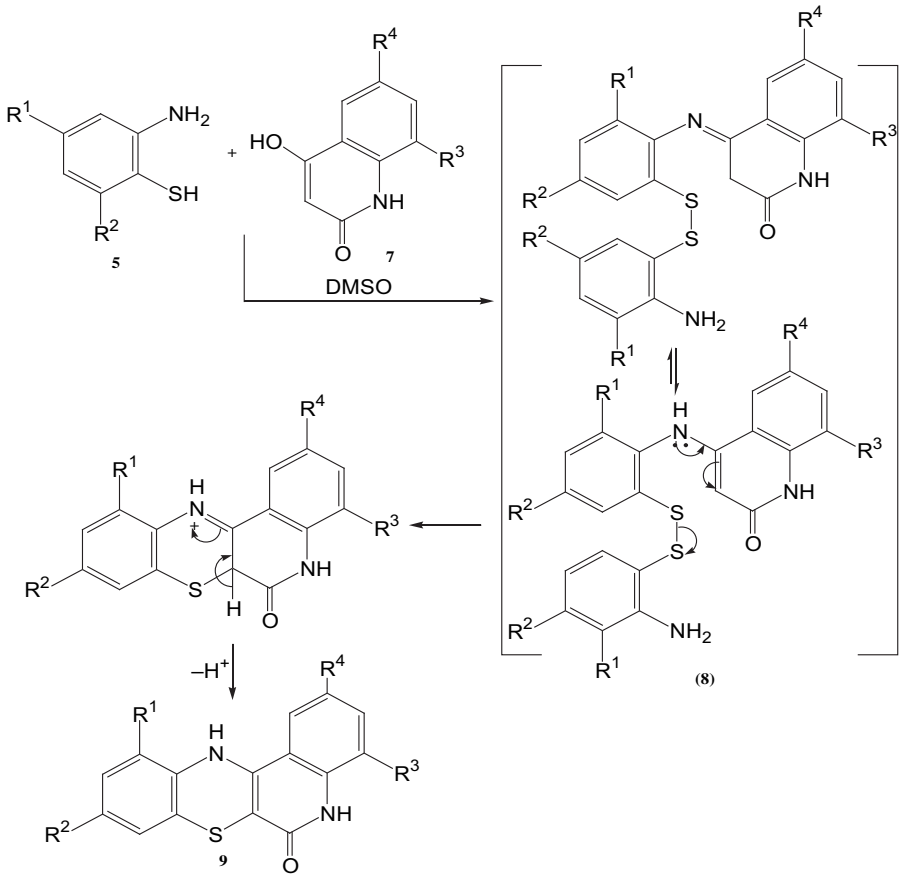
In the present work, a series of six new compounds were synthesized and all the synthesized quinolinobenzothiazinones **9a**–**f** were screened for their antioxidant activity by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging and 2,2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{\bullet+}$) radical cation decolorizaton assays.

The results of DPPH• and ($ABTS^{\bullet+}$) inhibition by compounds **9a**–**f** are summarized in Table 1 and Fig. 1. In the present investigation, the compounds **9c**, **9d** and **9f** showed excellent percent inhibition of DPPH• activity (54.29 ± 0.05%, 53.82 ± 1.2%, 22.45 ± 0.06% respectively) and were the most effective DPPH radical scavengers. The percentages can be considered as a full absorbance inhibition of DPPH•, as after completing the reaction, the final solution always possessed some yellowish colour and, therefore, its absorbance inhibition compared to the colourless methanol solution could not reach 100% [34,35].

Another antioxidant activity screening method, i.e., ABTS radical cation decolorization assay, showed results similar to those obtained by DPPH• assay. The compounds **9c**, **9d** and **9f** were the most active as they nearly fully scavenged ($ABTS^{\bullet+}$). The absorbance after 6 min were 0.052, 0.095 and 0.318 respectively. It was observed that the reaction with ($ABTS^{\bullet+}$) was fast in almost all the cases and completed within 1 min. During the remainder of the reaction time, the changes in absorbance were negligible. Thus, compounds **9c**, **9d** and **9f** showed the highest radical scavenging activities (Fig. 1).




**Scheme 2.** Synthesis of 4-hydroxyquinolin-2-ones.

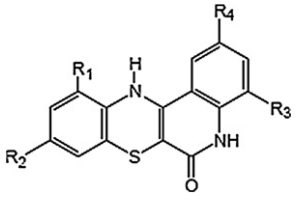



**9a**; $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$, $R_4 = H$
**9b**; $R_1 = CH_3$, $R_2 = H$, $R_3 = H$, $R_4 = CH_3$
**9c**; $R_1 = OCH_3$, $R_2 = H$, $R_3 = OCH_3$, $R_4 = H$
**9d**; $R_1 = H$, $R_2 = Br$, $R_3 = OCH_3$, $R_4 = H$
**9e**; $R_1 = H$, $R_2 = Br$, $R_3 = H$, $R_4 = CH_3$
**9f**; $R_1 = CF_3$, $R_2 = H$, $R_3 = H$, $R_4 = CH_3$

**Scheme 3.** Reaction sequence for the synthesis of quinolinobenzothiazinones.

A significant increase in liver reduced glutathione (GSH) content along with decrease in lipid peroxidation (LPO) level was observed in animals treated with compounds **9a**–**f** (Table 2). However, treatment with compound **9d** and **9e** showed highly significant increase in GSH contents ($P < 0.005$). Treatment with compounds **9a**, **9c** and **9f** showed comparatively less significant increase ($P < 0.05$) in GSH content over the normal (Fig. 2). Also, significant ($P < 0.05$) decrease in lipid peroxidation (LPO) level was observed in animals treated with the synthesized compounds (Fig. 3).

**Table 1**
Antioxidant activity of synthesized quinolinobenzothiazinones (DPPH• & ABTS•+ assays).



| S. No. | DPPH• % inhibition of 1 mg/ml of the compound | ABTS•+ activity at different time intervals (minutes) | | | | |
|---|---|---|---|---|---|---|
| | | 0 min | 1 min | 2 min | 4 min | 6 min |
| **9a** | 2.707 ± 0.03 | 0.722 | 0.620 | 0.610 | 0.610 | 0.610 |
| **9b** | 8.33 ± 0.02 | 0.721 | 0.560 | 0.520 | 0.520 | 0.520 |
| **9c** | 54.29 ± 0.05 | 0.726 | 0.055 | 0.052 | 0.052 | 0.052 |
| **9d** | 53.82 ± 1.2 | 0.725 | 0.141 | 0.098 | 0.098 | 0.095 |
| **9e** | 13.69 ± 0.09 | 0.724 | 0.412 | 0.406 | 0.406 | 0.406 |
| **9f** | 22.45 ± 0.06 | 0.722 | 0.328 | 0.318 | 0.318 | 0.318 |

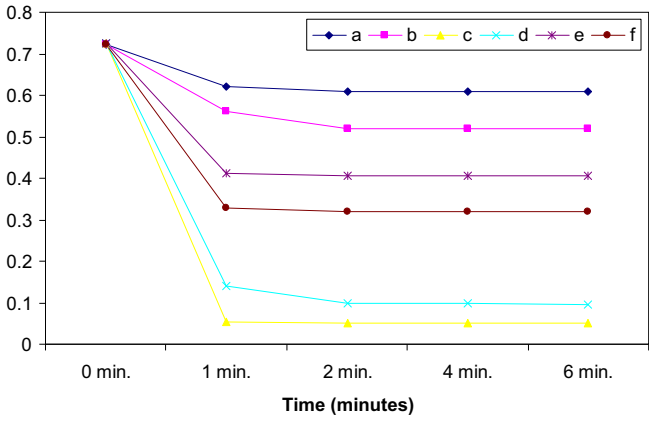
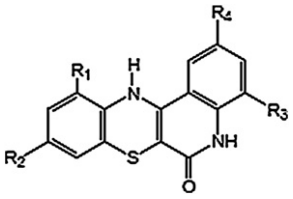



**Fig. 1.** ABTS activity at different time intervals by quinolinobenzothiazinones.

**Table 2**
Antioxidant properties of quinolinobenzothiazinones in the liver in Swiss Albino Mice (LPO & GSH).




| S. No. | LPO (*n* mole/mg tissue) | GSH (n mole/mg tissue) |
|---|---|---|
| **9a** | 6.72 ± 0.17, $P < 0.05$ | 4.51 ± 0.14, $P < 0.05$ |
| **9b** | 6.69 ± 0.16 | 4.50 ± 0.11 |
| **9c** | 6.81 ± 0.06, $P < 0.05$ | 4.80 ± 0.13, $P < 0.05$ |
| **9d** | 6.51 ± 0.16, $P < 0.05$ | 5.01 ± 0.09, $P < 0.005$ |
| **9e** | 6.42 ± 0.08, $P < 0.5$ | 5.0 ± 0.15, $P < 0.005$ |
| **9f** | 6.53 ± 0.17, $P < 0.5$ | 4.90 ± 0.25, $P < 0.05$ |

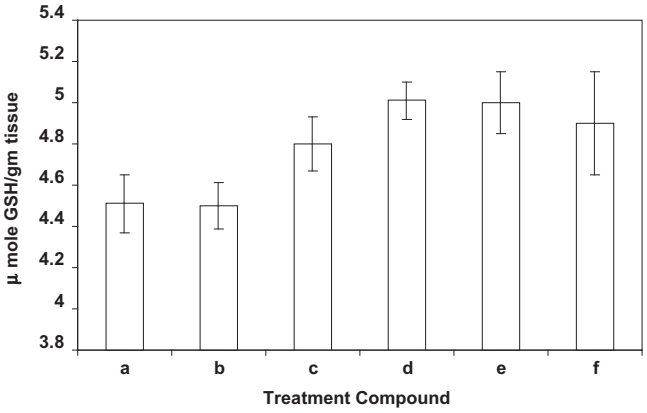



**Fig. 2.** Antioxidant influence of quinolinobenzothiazinones on GSH level in liver of Swiss albino mice.

## 4. Conclusion

In the present communication, quinolinobenzothiazinones have been synthesized by a simple and convenient method keeping in view multi-target drug design strategy with the annulation of heterocyclic structural pharmacophores. The synthesized compounds have been evaluated for their antioxidant activity by DPPH• and ABTS•$^+$ assays. The synthesized compounds **9c**, **9d** and **9f** have shown significant antioxidant activity as interpreted by the results of DPPH• and ABTS•$^+$ assays. The synthesized compounds have also shown interesting antioxidant activity as measured by estimating reduced glutathione (GSH) and lipid peroxidation (LPO) in liver of Swiss albino mice. The antioxidant activities of these compounds are attributed to the presence of quinolinobenzothiazine heterosystem (tetracyclic fused heterocycles with N–H bonds). Along with, we observed that the presence of substituents such as $CF_3$, $OCH_3$, $CH_3$ and Br on the aromatic ring also play an important role in deciding antioxidant activity.

## 5. Experimental protocols

### 5.1. Chemistry

The melting points of all the synthesized compounds were determined on the electrothermal melting point apparatus (PT-122) in open capillary tubes and are uncorrected. Substituted anilines were purchased from commercial sources and used without purification. The purity of all the compounds was checked by TLC. IR spectra were recorded on a Shimadzu 8400S FTIR spectrometer. $^1$H NMR and $^{13}$C NMR spectra were recorded on JEOL 300 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. The mass spectra of some of the synthesized compounds were provided by RSIC-CDRI (Lucknow). Analytical and spectral data of the synthesized compounds are included in the experimental section and are in agreement with the proposed structures of the synthesized compounds.

#### 5.1.1. General procedure for the synthesis of quinolino[3,4-b][1,4] benzothiazin-6(5H)-ones

To the stirred suspension of 4-hydroxyquinolin-2-one (0.01 mol) in DMSO (6 ml) was added substituted 2-aminobenzenethiol (0.01 mol) and the resulting mixture was refluxed for 1 h. The

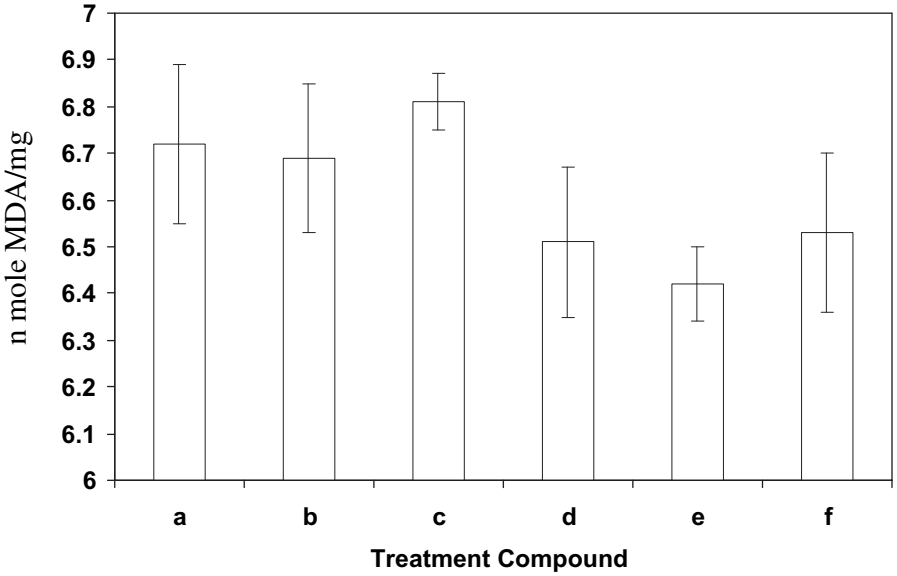



**Fig. 3.** Antioxidant influence of quinolinobenzothiazinones on LPO content in liver of Swiss albino mice.

mixture was cooled down to room temperature and the product separated was filtered and crystallized from methanol.

*5.1.2. 4,11-Dimethyl-6,12-dihydroquinolino[3,4-b][1,4] benzothiazin-6(5H)-one (**9a**)*

Yield: 65%, m.p.: 286–288 °C, IR (KBr) ($cm^{-1}$): 3410, 3330, 2900, 1682, 1624, 1494, 818. $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.36 (3H, s, $CH_3$), 2.54 (3H, s, $CH_3$), 6.90–7.89 (6H, m, Ar-H), 8.35 (NH), 10.80 (CONH). $^{13}$C NMR (DMSO-$d_6$) $\delta$ (ppm): 17.41, 18.09, 115.92, 116.54, 119.95, 121.29, 122.19, 122.46, 122.82, 127.55, 132.20, 133.28, 135.02, 147.57, 170.40. MS (*m*/*z*): 294 [$M^+$]; Anal. calcd. for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C 69.38; H, 4.76; N, 9.50.

*5.1.3. 2,11-Dimethyl-6,12-dihydroquinolino[3,4-b][1,4] benzothiazin-6(5H)-one (**9b**)*

Yield: 68%, m.p.: 284–287 °C, IR (KBr) ($cm^{-1}$): 3410, 3340, 2890, 1685, 1622, 1492, 816. $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.31 (3H, s, $CH_3$), 2.50 (3H, s, $CH_3$), 7.02–7.53 (6H, m, Ar-H), 8.41 (1H, s, NH), 10.91 (1H, s, CONH). $^{13}$C NMR (DMSO-$d_6$) $\delta$ (ppm): 17.42, 18.09, 115.92, 116.55, 119.95, 121.29, 122.19, 122.45, 122.82, 127.55, 132.20, 133.29, 135.01, 147.57, 170.41. MS (*m*/*z*): 294 [$M^+$], Anal. calcd. for $C_{17}H_{14}N_2OS$; C, 69.36; H, 4.79; N, 9.52, Found: C, 69.39; H, 4.78; N, 9.54.

*5.1.4. 4,11-Dimethoxy-6,12-dihydroquinolino[3,4-b][1,4] benzothiazin-6(5H)-one (**9c**)*

Yield: 70%, m.p.: 292–294 °C, IR (KBr) ($cm^{-1}$): 3390, 3325, 2880, 1680, 1610, 1490, 1250, 810. $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 3.84 (3H, s, $OCH_3$), 4.12 (3H, s, $OCH_3$), 6.89–7.91 (6H, m, Ar-H), 8.53 (1H, s, NH), 11.73 (1H, s, CONH). $^{13}$C NMR (DMSO-$d_6$) $\delta$ (ppm): 54.6, 55.7, 110.60, 115.86, 119.96, 120.24, 122.32, 122.42, 127.56, 133.24, 135.23, 121.24, 147.54, 156.0, 158.26, 169.60. MS (*m*/*z*): 326 [$M^+$]; Anal. calcd. for $C_{17}H_{14}N_2O_3S$; C, 62.56; H, 4.32; N, 8.58, Found: C, 62.57; H, 4.29; N, 8.60.

*5.1.5. 9-Bromo-4-methoxy-6,12-dihydroquinolino [3,4-b][1,4] benzothiazin-6(5H)-one (**9d**)*

Yield: 75%, m.p.: 298–300 °C, IR (KBr) ($cm^{-1}$): 3455, 3330, 2925, 1682, 1645, 1530, 1252, 835, 550. $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 3.89 (3H, s, $OCH_3$), 6.95–7.69 (6H, m, Ar-H), 8.89 (1H, s, NH), 11.70 (1H, s, CONH). Anal. calcd. for $C_{16}H_{11}BrN_2O_2S$; C 51.21, H 2.95, N 7.47; Found: C 51.33, H 2.96, N 7.48.

*5.1.6. 9-Bromo-2-methyl-6,12-dihydroquinolino [3,4-b][1,4] benzothiazin-6(5H)-one (**9e**)*

Yield: 72%, m.p.: 296–298 °C, IR (KBr) ($cm^{-1}$): 3460, 3340, 2940, 1688, 1650, 1550, 845, 560. $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.37 (3H, s, $CH_3$), 6.98–7.75 (6H, m, Ar-H), 8.55 (1H, s, NH), 10.68 (1H, s, CONH). Anal. calcd. for $C_{16}H_{11}BrN_2OS$; C, 53.49, H, 3.09, N, 7.80; Found: C, 53.63, H, 3.12, N, 7.82.

*5.1.7. 2-Methyl-11-trifluoromethyl-6,12-dihydroquinolino [3,4-b] [1,4] benzothiazin-6 (5H)-one (**9f**)*

Yield: 60%, m.p.: 294–296 °C, IR (KBr) ($cm^{-1}$): 3450, 3350, 2930, 1686, 1640, 1535, 1130, 840. $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.39 (3H, s, $CH_3$), 7.0–7.86 (6H, m, Ar-H), 8.59 (1H, s, NH), 10.89 (1H, s, CONH). Anal. calcd. for $C_{17}H_{11}F_3N_2OS$; C, 58.62, H, 3.18, N, 8.04, Found: C, 58.66; H, 3.20, N, 8.10.

*5.2. Pharmacology*

*5.2.1. DPPH radical scavenging assay*

Radical scavenging activity of the compounds **9a**–**f** was determined against stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical spectrophotometrically [36]. A stock solution (1 mg/ml) of the compound was prepared in methanol. 50 μl of the compounds were added to 5 ml of a 0.004% methanol solution of DPPH radical. After 30 min of incubation in dark at room temperature, the absorbance was observed against a blank at 517 nm.

The assay was carried out in triplicate and the percentage of inhibition was calculated using the following formula.

$$\%\ \text{Inhibition} = \frac{(AB - AA)}{AA} \times 100$$

where, AB = absorption of blank and AA = absorption of test

*5.2.2. ABTS radical cation decolorization assay*

The 2,2-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) radical cation ($ABTS^{\bullet+}$) decolorization test [37] was also used to evaluate the antioxidant activity of compounds **9a**–**f**. ($ABTS^{\bullet+}$) was generated by oxidation of ABTS with potassium persulphate. For this purpose, ABTS was dissolved in deionized water to 7 mM concentration, and potassium persulphate was added to a concentration of 2.45 mM. The reaction mixture was left at room temperature overnight (12–16 h) in the dark before its use. The ($ABTS^{\bullet+}$) solution was then diluted with ethanol to an absorbance of 0.700 ± 0.020 at 734 nm. After addition of 1 ml of the diluted ($ABTS^{\bullet+}$) solution (A 734 nm = 0.700 ± 0.020) to 10 μl of the compound, the absorbance readings were taken at 30 °C at intervals of exactly 1–6 min after mixing later. All determinations were carried out in triplicate.

*5.2.3. In vivo studies in Swiss albino mice*

The compounds were further treated for evaluation of antioxidative properties in Swiss albino mice. Results showed that there was significant decrease in lipid peroxidation (LPO) level and elevation in reduced glutathione (GSH) in Swiss albino mice.

*5.2.3.1. Material and methods*

*5.2.3.1.1. Animals.* Swiss albino mice were obtained from Jawaharlal Nehru University, New Delhi, India. Rendom-bred, Males Swiss albino mice weighing 24 ± 2 g were used for experiments. These animals were maintained in the animal house at temperature of 24°±3 °C.

The mice were obtained in two groups. Group-I animals were fed orally with 0.1 ml of double-distilled water once a day for 7 days before radiation and served as the control group, while animal of Group-II received compound in 0.1 ml of double-distilled water in a similar fashion.

Animals were sacrificed by cervical dislocation and liver was perfused in situ immediately with cold 0.9% NaCl and thereafter carefully removed and rinsed in chilled 0.15 ml tris KCl buffer (pH 7.4) to yield a 10% (w/v) homogenate. Aliquots (0.5 ml) of this homogenate were used for assaying reduced glutathione and lipid peroxidation.

*5.2.3.1.2. Chemicals.* Synthesized quinolinobenzothiazinones DPPH, (2,2-diphenyl-1-picrylhydrazyl), ABTS (2,2-azinobis) 3-ethylbenzothiozoline-6-sulfonic acid, potassium persulphate, trichloroacetic acid (TCA), 5-dithiobis-2-nitrobenzoic acid (DTNB), thiobarbituric acid (TBA), etc.

*5.2.3.2. Biochemical studies*

*5.2.3.2.1. Lipid peroxidation.* Lipid peroxidation level in liver was estimated spectrophotometrically by thiobarbituric acid – reactive substances (TBARS) method of Ohkhawa [38] and expressed in terms of malondialdehyde formed per mg protein. In brief, 0.4 ml of microsomal sample was mixed with 1.6 ml of 0.15 M tris KCl buffer to which 0.5 ml of 30% TCA was added. Then 0.5 ml of 52 mM TBA was added and mixture placed in a water bath for 25 min at 80 °C, cooled in ice and centrifuged at room temperature for 10 min at 3000 rpm. The absorbance of the clear supernatant was measured against a reference blank of distilled water at 531.8 nm.

*5.2.3.2.2. Reduced glutathione.* Reduced glutathione (GSH) level was determined by the method described by Moron [39]. Homogenates were immediately precipitated with 0.1 ml 25%. TCA and the precipitate were removed after centrifugation. Free-SH groups were assayed in a total 3 ml volume by the addition of 2 ml of 0.6 mM DTNB and 0.9 ml 0.2 mM sodium phosphate buffer (pH 8.0) to 0.1 ml of supernatant and the absorbance was observed at 412 nm using a UV–vis systronics spectrophotometer. Glutathione was used as a standard to calculate μmol GSH/g tissue.

*5.2.3.3. Statistical analysis.* Results of the biochemical studies were evaluated using student's '*t*' test.

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