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Design, Synthesis and Antioxidant activity of Quinazoline-based Aminothiazole Hybrids

Sateesh Amudala and Jyothi Mandala*

Department of Chemistry and Pharmaceutical sciences, Mahatma Gandhi University, Nalgonda-508254, **INDIA**

Email: jyothimandala2022@gmail.com

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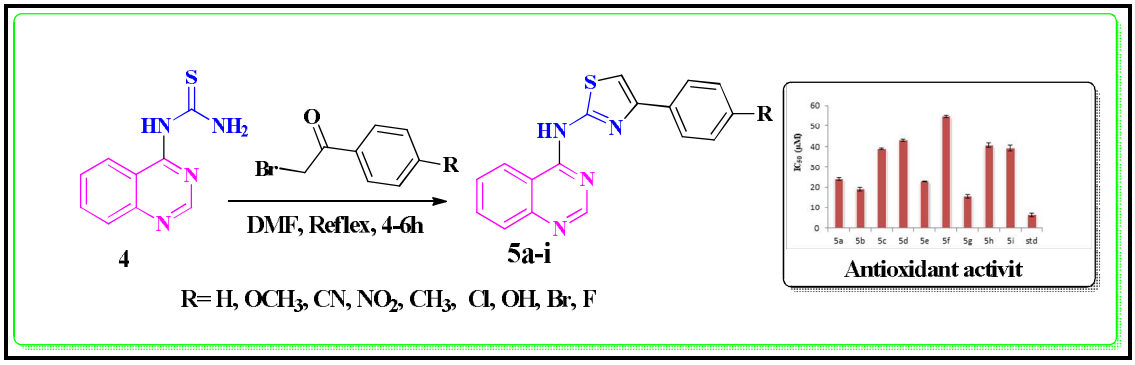
ABSTRACT

*This research represents the synthesis of a novel series of Quinazoline-based aminothiazole analogues (5a-i). All the synthesized compounds were described using ^{1}H NMR, ^{13}C NMR, ESI-mass spectrum and elemental analysis. The synthesized compounds were investigated for antioxidant activity. The compounds **5g** and **5b** displayedmore potent antioxidant activity, and **5e** showed good activity when compared with ascorbic acid, as a standard drug.*

Graphical Abstract



Keywords: Quinazoline-based aminothiazole, DPPH, Antioxidant activity.

INTRODUCTION

Quinazolinones are a type of heterocyclic structure that is very important.It's a bicyclic compound having a pyrimidine system fused to a benzene ring at positions 5 and 6. In medicinal chemistry, they constitute one of the most important categories of heterocycles [**1**]. They have a variety of biological activities like analgesic, anticancer, anti-HIV, antifungal, antibacterial, anticonvulsant, antioxidant, anti-inflammatory, antispasmolytic, anticoagulant, antiangiogenesis, and anti-invasive properties [**2-14**]. Many marketed drugs contain a quinazolinone moiety, such as an antifungal agent, albconazoleis used, Selurampanel is a drug used to treat epilepsy, Linagliptin is a drug used to treat type 2 diabetes,

the thymidylate synthase inhibitor nolatrexed and Gifitinib is a drug that is used to treat lung andbreast cancer.Quinazolinone derivatives have also become a major scaffold in pharmaceutical chemistry in recent years [**15-19**].

Thiazoles, on the other hand, are significant compounds that have a variety of biological properties. Thiazole substrates have a broad range of biological activities such as antitumor [**20**], antiviral [**21**], antitubercular [**22**], anticancer [**23**], antimalarial [**24**] antihypertensive [**25**], antifungal [**26**] and anti-HIV [**27**] activities. Multiple therapeutically active drugs such as vosaroxin, bleomycin, dasatinib, and epothilones belong to the thiazole scaffold, which has been shown to have anticancer properties [**28**]. Anticancer drugs that bind to grooves, like thia-netropsin, netropsin, and dactinomycin,all have a thiazole moiety in their structure [**29**]. In comparison to their parent chemicals, other 2-aminothiazole derivatives such as cantharidin [**30**] and giroline [**31**] showed increased apoptotic activity.This study describes the synthesis of a series of Quinazoline-based aminothiazole analogues (**5a-i**). These compounds were screened for their antioxidant activity.

MATERIALS AND METHODS

All the chemicals and reagents used were A.R Grade. The melting points were recorded using an Electro thermal melting point meter but are uncorrected. A Perkin-Elmer 2400 CHN analyzer was used to perform elemental analysis (% C, H, and N). Analytical thin layer chromatography (TLC) was used to check the reaction progress and the purity of the compounds, with Merck percolated Silica Gel 60F254 sheets (Darmstadt, Germany), by heptane-ethyl acetate 3:7 elution method, and UV light for visualization. In DMSO-d_6 as a solvent and tetramethylsilane as an internal standard, ^{1}H and ^{13}C NMR spectra were recorded on JEOL 400 MHz and 100 MHz, respectively. The mass spectra were recorded using Electrospray Ionization–Mass Spectrometry (ESI–MS).

General procedure for the synthesis of 4-chloroquinazoline (3): Quinazolin-4(3H)-ones (1 mmol) were partially added to a cooled stirring solution of $POCl_3$(10 mL) and N,N-dimethylaniline (0.5 mL). The mixture refluxed for 6 hours. After removing the excess $POCl_3$under vacuum, the residue was cooled, triturated with ice/water, and alkalinized with 2N sodium hydroxide.DCM was used to extract the aqueous solution 4-5 times. The mixed DCM extracts were dried over sodium sulfate (Na_2SO_4) and filtered, and the solvent was evaporated under reduced pressure. The produced solid crystallized from ethanol to produce compound **3**.

Synthesis of 1-(quinazolin-4-yl)thiourea (4): The compound 3 (1 mmol) was condensed with thiourea (1mmol) in the presence of ethanol for reflux overnight. After completion of the reaction mixture cooled at room temperature, the solid product was filtered and washed with ethanol to obtain a yellow solid product.

4-Phenyl-N-(quinazolin-4-yl)thiazol-2-amine (5a): A mixture of 1-(quinazolin-4-yl) thiourea **4** (1mmole) and α-bromo-4-substituted-acetophenones (1mmol) was refluxed in of DMF (10mL) for 4 h. The reaction mixture completion was monitored using TLC. The reaction mixture was cooled at room temperature; the solid separated out was filtered, washed with water and yielded an analytically pure product with recrystallization ethanol.

Solid; Yellow colour; Yield: 94%; mp: 244-246 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.56 (s, 1H, -NH), 8.93 (s, 1H, Quinazoline-H), 8.10 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar-H), 7.90 (dd, *J* = 16.3, 7.6, Hz, 2H, Ar-H), 7.73 (dd, *J* = 7.3, 1.2 Hz, 2H, Ar-H), 7.60(td, *J* = 7.5, 1.4 Hz, 1H, Ar-H), 7.49 (t, *J* = 7.3 Hz, 2H, Ar-H), 7.43 (dd, *J* = 5.3, 3.8 Hz, 1H, Ar-H), 7.23 (s, 1H, thiazole-H);^{13}C NMR (100 MHz,DMSO-d_6): δ 162.80, 154.66, 153.91, 153.09, 143.96, 134.63, 131.43, 130.20, 129.70, 127.68, 127.08, 126.15, 124.59, 113.56, 110.64; MS (ESI): m/z 305 $[M + H]^+$; Anal. calcd. for$C_{17}H_{12}N_4S$: C, 67.08; H, 3.97; N, 18.41; found: C, 67.15; H, 4.01; N, 18.23.

4-(4-Methoxyphenyl)-N-(quinazolin-4-yl)thiazol-2-amine (5b): Solid; Light yellow colour; Yield: 96%; mp: 220-222 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H, -NH), 9.02 (s, 1H, Quinazoline-H), 8.07 (dd, *J* = 7.4, 1.5 Hz, 1H, Ar-H), 7.90 – 7.80 (m, 2H, Ar-H), 7.70 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.59 (dd, *J* = 7.5, 1.3 Hz, 1H, Ar-H), 7.18 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.06 (s, 1H, thiazole-H), 3.81 (s, 3H, OCH_3);^{13}C NMR (100 MHz, DMSO-d_6): δ 163.02, 159.76, 154.12, 153.93, 153.11, 143.98, 131.46, 130.20, 128.83, 128.55, 126.10, 124.55, 115.28, 112.76, 110.46, 56.63;MS (ESI): m/z 335 $[M + H]^+$; Anal. calcd. for$C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75; found: C, 66.71; H, 4.16; N, 16.81.

4-(2-(Quinazolin-4-ylamino)thiazol-4-yl)benzonitrile (5c): Solid; Orange colour; Yield: 89%; mp: 248-250 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H, -NH), 9.05 (s, 1H, Quinazoline-H), 8.09 (dd, *J* = 7.4, 1.5 Hz, 1H, Ar-H), 7.89 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.80 (dd, *J* = 15.5, 7.6, Hz, 2H, Ar-H), 7.73 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.58 (td, *J* = 7.5, 1.4 Hz, 1H, Ar-H), 7.10 (s, 1H, thiazole-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.20, 154.40, 153.90, 153.13, 143.98, 136.88, 131.43, 130.16, 129.81, 127.91, 126.15, 124.53, 119.16, 115.43, 112.82, 110.56;MS (ESI): m/z 329 $[M]^+$; Anal. calcd. for$C_{18}H_{11}N_5S$: C, 65.64; H, 3.37; N, 21.26; found: C, 65.71; H, 3.16; N, 21.18.

4-(4-Nitrophenyl)-N-(quinazolin-4-yl)thiazol-2-amine (5d): Solid; Orange colour; Yield: 92%; mp: 264-266 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H, -NH), 8.93 (s, 1H, Quinazoline-H), 8.38 (d, *J* = 7.5 Hz, 2H, Ar-H), 8.07 (dd, *J* = 7.5, 1.3 Hz, 1H, Ar-H), 7.96 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.85 – 7.75 (m, 2H, Ar-H), 7.58 (td, *J* = 7.5, 1.4 Hz, 1H, Ar-H), 7.04 (s, 1H, thiazole-H);^{13}C NMR (100 MHz,DMSO-d_6): δ 163.40, 154.60, 153.93, 153.16, 148.03, 143.98, 138.77, 131.43, 130.14, 127.32, 126.15, 125.90, 124.52, 112.69, 110.54;MS (ESI): m/z 351 $[M + H]^+$; Anal. calcd. for$C_{17}H_{11}N_5O_2S$: C, 58.44; H, 3.17; N, 20.05; found: C, 58.21; H, 3.20; N, 20.13.

N-(Quinazolin-4-yl)-4-(p-tolyl)thiazol-2-amine (5e): Solid; Yellow colour; Yield 96%; mp: 236-238 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (s, 1H, -NH), 9.11 (s, 1H, Quinazoline-H), 8.11 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar-H), 7.80 (dd, *J* = 16.3, 7.6, Hz, 2H, Ar-H), 7.65 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.56 (td, *J* = 7.5, 1.4 Hz, 1H, Ar-H), 7.35 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.05 (s, 1H, thiazole-H), 2.56 (s, 3H, $-CH_3$);^{13}C NMR (100 MHz, DMSO-d_6): δ 163.46, 154.22, 153.91, 153.10, 143.95, 138.53, 134.28, 131.42, 130.34, 130.12, 127.71, 126.12, 124.50, 112.73, 110.39, 22.43;MS (ESI): m/z 319 $[M + H]^+$; Anal. calcd. for$C_{18}H_{14}N_4S$: C, 67.90; H, 4.43; N, 17.60; found: C, 68.01; H, 4.36; N, 17.54.

4-(4-Chlorophenyl)-N-(quinazolin-4-yl)thiazol-2-amine (5f): Solid; Yellow colour; Yield 86%; mp: 260-262 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H, -NH), 8.96 (s, 1H, Quinazoline-H), 8.12 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar-H), 7.85 – 7.74 (m, 2H, Ar-H), 7.64 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1H, Ar-H), 7.47 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.10 (s, 1H, thiazole-H);^{13}C NMR (100 MHz,DMSO-d_6): δ 163.49, 154.36, 153.89, 153.10, 143.89, 134.53, 133.95, 131.40, 130.17, 129.57, 128.65, 126.16, 124.55, 112.63, 110.51;MS (ESI): m/z 339 $[M + H]^+$; Anal. calcd. for$C_{17}H_{11}ClN_4S$: C, 60.26; H, 3.27; N, 16.54; found: C, 60.33; H, 3.18; N, 16.62.

4-(2-(Quinazolin-4-ylamino)thiazol-4-yl)phenol (5g): Solid; Light yellow colour; Yield: 93%; mp: 232-234 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H, -NH), 8.97 (s, 1H, Quinazoline-H), 8.09 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar-H), 7.86 (dd, *J* = 16.3, 7.5 Hz, 2H, Ar-H), 7.62 – 7.51 (m, 3H, Ar-H), 7.19 (d, *J* = 7.2 Hz, 2H, Ar-H), 6.98 (s, 1H, thiazole-H), 5.68 (s, 1H, -OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.41, 158.43, 154.59, 153.89, 153.14, 143.96, 131.40, 130.10, 128.60, 126.13, 125.40, 124.53, 117.01, 112.69, 110.54;MS (ESI): m/z 321 $[M + H]^+$; Anal. calcd. for$C_{17}H_{12}N_4OS$: C, 63.73; H, 3.78; N, 17.49; found: C, 63.68; H, 3.81; N, 17.52.

4-(4-Bromophenyl)-N-(quinazolin-4-yl)thiazol-2-amine (5h): Solid; Pale yellow colour; Yield: 90%; mp: 254-256 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H, -NH), 8.99 (s, 1H, Quinazoline-H), 8.09 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar-H), 7.84 – 7.75 (m, 2H, Ar-H), 7.65 – 7.55 (m, 5H, Ar-H), 7.09 (s, 1H, thiazole-H);^{13}C NMR (100 MHz, DMSO-d_6): δ 163.43, 154.58, 153.89, 153.10,

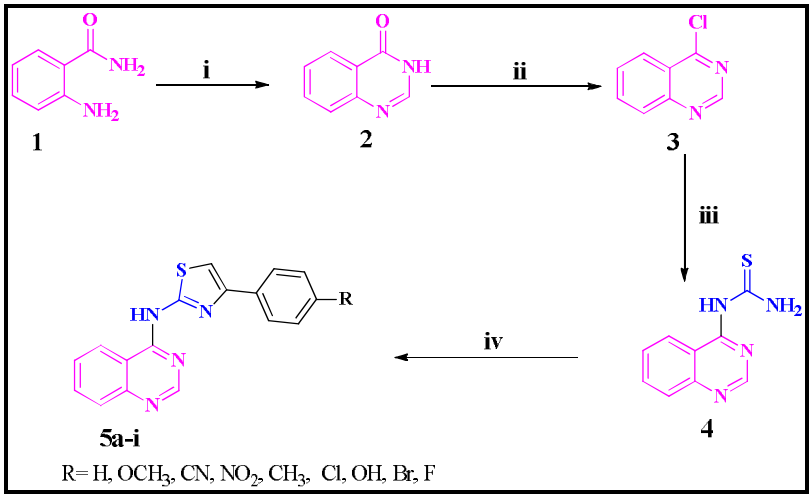
143.95, 133.87, 132.73, 131.45, 130.14, 127.20, 126.15, 125.30, 124.50, 112.68, 110.54;MS (ESI): m/z 383 $[M + 2]^+$; Anal. calcd. for$C_{17}H_{11}BrN_4S$: C, 53.27; H, 2.89; N, 14.62; found: C, 53.32; H, 2.81; N, 14.56.

4-(4-Fluorophenyl)-N-(quinazolin-4-yl)thiazol-2-amine (5i): Solid; Yellow colour; Yield: 92%; mp: 232-234 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.94 (s, 1H, -NH), 9.04 (s, 1H, Quinazoline-H), 8.11 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar-H), 7.85 – 7.76 (m, 2H, Ar-H), 7.69 (dd, *J* = 7.5, 5.1 Hz, 2H, Ar-H), 7.61 (td, *J* = 7.5, 1.4 Hz, 1H, Ar-H), 7.20 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.10 (s, 1H, thiazole-H); ^{13}C NMR (100 MHz,DMSO-d_6): δ 164.62, 163.42, 162.04, 154.60, 153.93, 153.13, 143.98, 131.38, 130.14, 129.59, 126.12, 124.52, 116.99, 112.71, 110.50;MS (ESI): m/z 323 $[M + H]^+$; Anal. calcd. for$C_{17}H_{11}FN_4S$: C, 63.34; H, 3.44; N, 17.38; found: C, 63.39; H, 3.52; N, 17.46.

Antioxidant activity: The synthesized titled compounds (5a-i) were examined for *in vitro* antioxidant activity in terms of radical scavenging ability by rapid comfortable technique Brand *Williams* method, i.e. DPPH (1,1-diphenyl-2-picryl-hydrazyl) assay using Ascorbic acid as the standard drug. As a blank, control and reference, we used 95% methanol, DPPH solution and standard drug (ascorbic acid) respectively. Using the serial dilution process, 10^{-6} molar ratios of synthesized compounds were prepared in methanol solution in this experiment.1 mL of a mixture of different concentrations (50, 100, 150, 200 µg mL^{-1}) of the scaffold 100 µL, 10^{-4}molar DPPH radical solution 900 µL were placed in small test tubes and incubated at 37°C for 30 minutes under dark conditions [32]. Using a UV-Visible spectrophotometer, the color transition from blue to yellow was observed, and absorbance was measured at 517 nm (at DPPH's absorption maximum). All the samples were checked three times to ensure precision and determine standard deviation. In this regard, free radicals are produced by the DPPH molecule, which is then scavenged by the synthesized compounds. The lesser the absorbance value indicates the increased radical scavenging activity of the test compounds [33]. Antioxidant analysis was assessed in IC_{50} in µM [34].

RESULTS AND DISCUSSION

The synthesis method for the desired compounds is displayed in Scheme 1. Initial from 2-amino-benzamide (**1**) intermediates**2, 3** were synthesized in better yields according to the synthetic protocols [35-37]. The compound **3** was further converted to 1-(quinazolin-4-yl)thiourea (**4**) via an overnight reaction with thiourea in an ethanol solvent. Finally intermediate **4** again cyclic condensations with α-bromo-4-substituted-acetophenones in DMF solvent in reflux condition afforded the target compounds **5a-i** in acceptable yields.



Scheme 1. Synthesis of Quinazoline-based aminothiazoles (**5a-i**). Reagent and Conditions: (i) Ar-CHO/DMF/I_2/K_2CO_3/70–90°C/4–5 h. (ii) $POCl_3$/N,Ndimethylaniline/reflux 6 h. (iii) Thiourea/ethanol/overnight. (iv) α-bromo-4-substituted-acetophenones/DMF/4-6h.

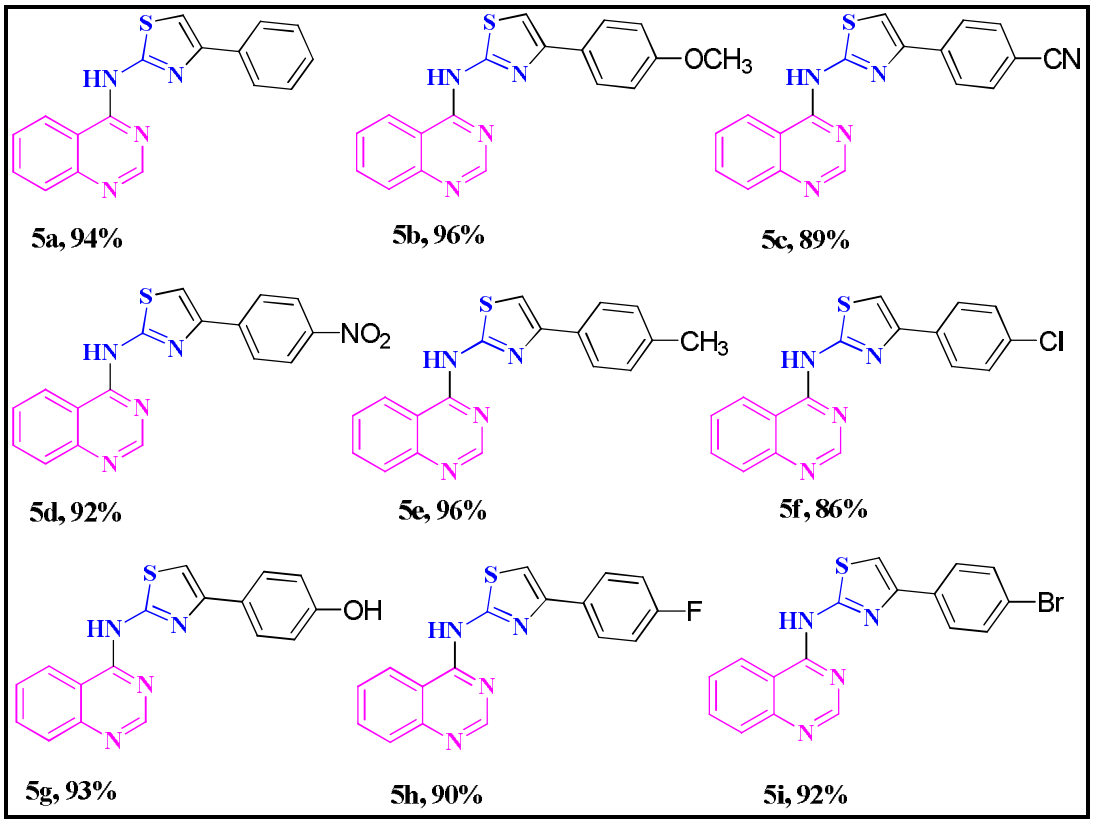


Figure 1. Synthesized Quinazoline-based aminothiazole analogues.

All the final scaffolds are fully identified by ^{1}H and ^{13}C NMR, ESI- mass spectrometry, and elemental analysis. The ^{1}NMR spectrum of compound **5a** displayed three singlet peaks at 11.56 ppm with an amino proton, 8.93 ppm with a Quinazoline-C2 proton and 7.23 ppm with a thiazole-C5 proton, and the remaining protons are aromatic regions. The ^{13}C NMR spectrum of compound 5a shows the peaks belonging to quinazoline-C4 carbon at 162.80 ppm, quinazoline-C9 carbon at 154.66 ppm, thiazole-C2 carbon at 153.91 ppm, quinazoline-C2 carbon at 153.09 ppm, and thiazole-C5 carbon at 110.64 ppm. The remaining carbons are aromatic regions. ESI-Mass spectra show the presence of a [M + H] ion peak at m/z: 305. The elemental analysis (CNH) data (C, 67.15; H, 4.01; N, 18.23) was confirmed by the chemical formula ($C_{17}H_{12}N_4S$) of compound **5a** (Figure 1).

Antioxidant activity: All the synthesized Quinazoline-based aminothiazole scaffolds (**5a-i**) were examined for free radical scavenging activity and radical scavenging ability in terms of the DPPH approach [38]. DPPH solution, MeOH (95%), and ascorbic acid were used in control, black, and reference, respectively. The Quinazoline-based aminothiazoles were tested in triplicate, and the standard deviation was calculated. The IC_{50} (µM) values are shown in table 1 and figure 2.

The activity results revealed that the compounds 5g and 5b exhibited more potent activity with an IC_{50} value of 15.73 ± 0.87 µM and 19.03 ± 0.95 µM compared with the standard drug ascorbic acid, with an IC_{50} value of 6.28 ± 0.86 µM, respectively. The compound 5e shows good antioxidant activity with IC_{50} value of 22.83 ± 0.14 µM, respectively. The remaining compounds exhibited poor activity values ranging from 24.09 ± 0.66µM to 54.85 ± 0.54 µM.The antioxidant activity of all the synthesized derivatives (**5a-i**) mainly dependson the type of substituted phenyl ring on the thiazole moiety. The compounds **5g,5b** and **5e** potent activity due to the presence of hydroxyl, methoxy and methyl groups substituents on the thiazole phenyl ring, which may enhance the antioxidant activity.

Table 1. Antioxidant activity of the Quinazoline-based aminothiazoles(**5a–i)** by DPPH method

S.No	Compounds	IC_{50} (µM)
1	5a	24.09 ± 0.66
2	**5b**	**19.03 ± 0.95**
3	5c	38.92 ± 0.32
4	5d	43.08 ± 0.06
5	**5e**	**22.83 ± 0.14**
6	5f	54.85 ± 0.54
7	**5g**	**15.73 ± 0.87**
8	**5h**	**40.78 ± 0.93**
9	5i	39.42 ± 1.29
Standard	**Ascorbic acid**	**6.28 ± 0.86**

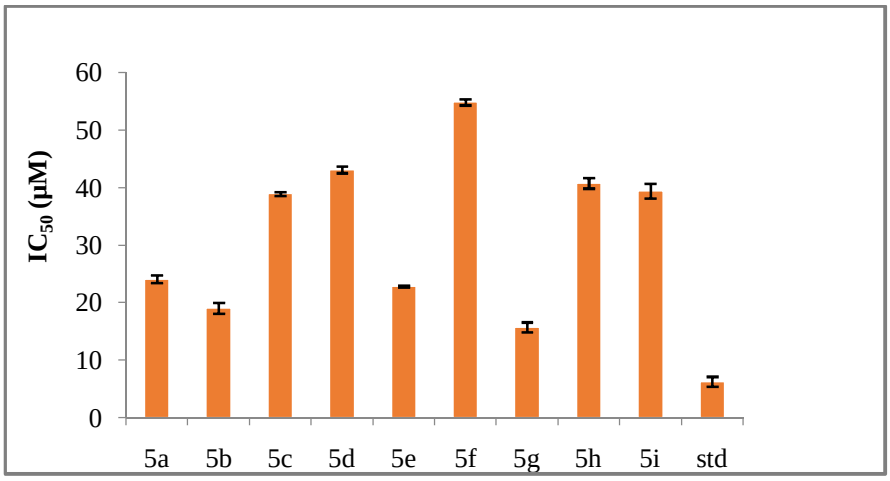


Figure 2. Antioxidant activity of the Quinazoline-based aminothiazoles (**5a-i**).

APPLICATION

All the synthesized Quinazoline-based aminothiazole analogues were evaluated for antioxidant activity. These analogues identified in this study indicate exciting possibilities for developing new antioxidant agents.

CONCLUSION

A series of novel Quinazoline-based aminothiazole analogues (**5a-i**) were synthesized. The structures of newly synthesized compounds were confirmed using basic spectral analysis such as ^{1}H NMR, ^{13}C NMR, ESI-mass spectrum, and CHN analysis. These compounds were examined for their DPPH free radical scavenging ability. The compounds **5g** and **5b** exhibited excellent activity with IC_{50} values of 15.73 ± 0.87 µM and 19.03 ± 0.95 µM, respectively. The compound **5e** showed good antioxidant activity with IC_{50} value of 22.83 ± 0.14 µM, compared with the standard drug ascorbic acid, with an IC_{50} value of 6.28 ± 0.86 µM, respectively.

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