International Journal of Pharmacy and Pharmaceutical Sciences
ISSN- 0975-1491 Vol 2, Suppl 4, 2010

Research Article

SYNTHESIS AND EVALUATION OF ANTIOXIDANT ACTIVITIES OF NOVEL QUINAZOLINONE DERIVATIVES

GOVINDARAJ SARAVANAN*, VEERACHAMY ALAGARSAMY[1] AND CHINNASAMY RAJARAM PRAKASH[2]

*Medicinal Chemistry Research Laboratory, Bapatla College of Pharmacy, Bapatla-522101 (A.P), India., [1]Medicinal Chemistry Research Laboratory, M.N.R. College of Pharmacy, Sangareddy-502294 (A.P), India, [2]Department of Pharmaceutical Chemistry, D.C.R.M. Pharmacy College, Inkollu-523167 (A.P), India. Email: sarachem1981@gmail.com

Received: 04 Jun 2010, Revised and Accepted: 05 July 2010

ABSTRACT

In the present study, a novel quinazolin-4-(3H)-ones were synthesized by condensation of 2-amino-4-phenylthiazole/2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene with 6,8-(un/mono/di)-bromo-2-(methyl/phenyl)-4H-benzo-[1,3]-oxazine-4-ones. The 2-amino-4-phenyl-thiazole and 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene was synthesized from acetophenone and cyclohexanone respectively. The 6,8-(un/mono/di)-bromo-2-(methyl/phenyl)-4H-benzo-[1,3]-oxazine-4-ones were synthesized from 3,5-(un/mono/di)-bromo anthranilic acid. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR, Mass spectral and Elemental analysis. These compounds were screened for anti-oxidant activity by DPPH radical scavenging activity method. 6,8-Dibromo-2-phenyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one **(7i)** exhibited highest scavenger activity among the synthesized compounds. Phenyl derivatives exhibited more activity than methyl derivative. In addition, brominated compound exhibited better activity than unsubstituted one

Keywords: Quinazolin-4-(3H)-one, Thiazole, Benzothiophene and Anti-oxidant.

INTRODUCTION

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Quinazolin-4(3H)-ones[1-5] are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological activities such as, anti-microbial, anti-cancer, anti-convulsant, anti-tubercular, etc. In addition, several physiological activities such as anti-bacterial, fungicidal, anti-spasmodic, analgesic and anti-tubercular of various thiazole[6-8] derivatives have proved their efficacy in combating variety of diseases. A large number of benzothiophene[9-11] derivatives have been found to exhibit a wide variety of pharmaceutical activity such as anti-microbial, anti-cancer and anti-HIV.

The search for new molecules with anti-oxidant properties is a very active domain of research, since they can protect the human body from free radicals and retard the progress of many chronic diseases, such as vascular diseases, some forms of cancer and oxidative stress responsible for DNA, protein and membrane damage. Reactive oxygen species (ROS) such as superoxide anions, hydrogen peroxide, hydroxyl and nitric oxide radicals, play an important role in oxidative stress related to the pathogenesis of various important diseases[12]. Anti-oxidants act as a major defense against radical mediated toxicity by protecting the damages caused by free radicals. Anti-oxidants agents are effective in the prevention and treatment of complex diseases, like atherosclerosis, stroke, diabetes, Alzheimer's disease and cancer[13]. Flavonoids and phenolic compounds are widely distributed in plants which have been reported to exert multiple biological effects including anti-oxidants, free radical scavenging abilities, anti-inflammatory and anti-carcinogenic[14]. This has attracted a great deal of research interest in natural anti-oxidants. A number of synthetic compounds such as quinazolinones[15], thiazoles[16] and benzothiophene[17] have also been extremely exploited for anti-oxidants activity. The above observation stimulated our interest to; synthesize a series of compounds containing quinazolin-4(3H)-one ring system associated with thiazole/benzothiophene moiety and to evaluate their anti-oxidant potency.

MATERIALS AND METHODS

1,-1-diphenyl-2-picryl-hydrazine (DPPH) was purchased from Sigma-Aldrich (St. Louis, USA). Ascorbic acid and methanol were purchased from E-Merck (Darmstadt, Germany). The remaining solvents and other chemicals were of purchased from Sigma-Aldrich (St. Louis, USA). The melting points were determined on a MEL-Temp apparatus by open capillary tube method and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FT-IR spectrometer MB 104 with KBr pellets. The ^{1}H-NMR (300 MHz) spectra were recorded on a Bruker 300 NMR spectrometer with TMS as internal references. Mass spectra were recorded on Shimadzu GC MS QP 5000. Microanalyses were obtained with an elemental Analyses system GmbH VarioEL V300 element analyzer. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF_{254}, 200 mesh) aluminium plates ((E-Merck, Darmstadt, Germany) using ethyl acetate: n-hexane as developing solvent and visualized in UV chamber. IR, ^{1}H-NMR, Mass spectra and Elemental analysis were consistent with the assigned structures.

Chemistry

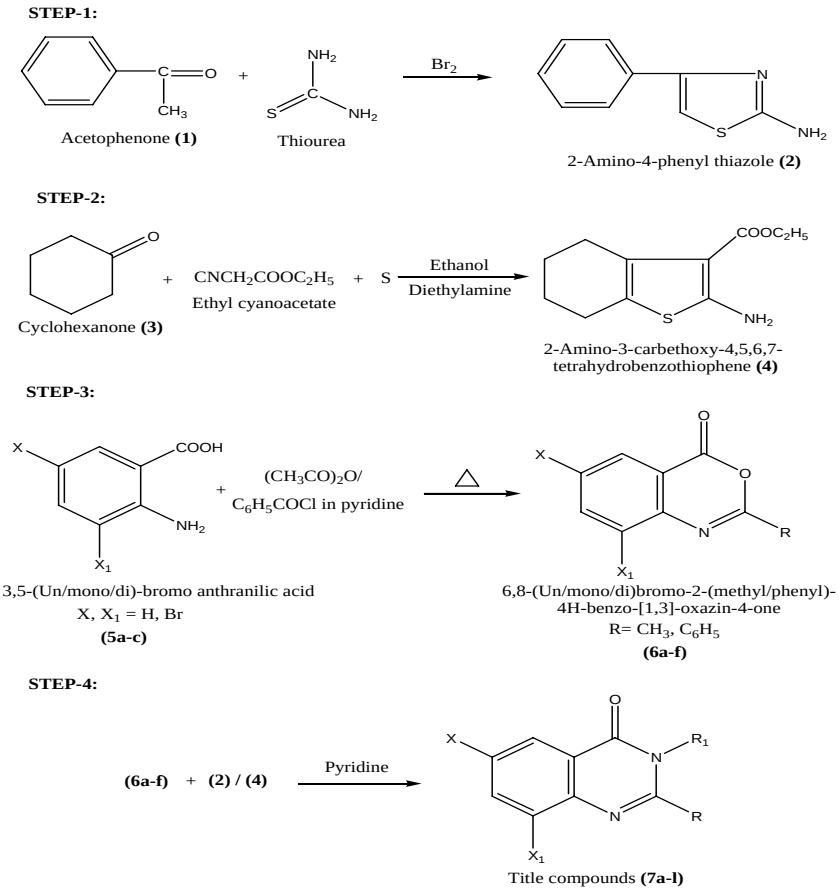
The synthetic strategy to synthesize the title compounds (7a-l) is depicted in scheme - 1. In step 1, acetophenone (1) is allowed to react with thiourea in presence of bromine to produce 2-amino-4-phenyl thiazole (2). In step 2, cyclohexanone (3) was subjected to condensed with ethylcyanoacetate and sulphur to produce 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene (4). In step 3, 3,5-(un/mono/di)-bromo anthranilic acid (X, X_1 = H/Br) (5) were allowed to react with acetic anhydride/benzoyl chloride in dry pyridine for cyclization to produce 6,8-(un/mono/di)-bromo-2-(methyl/phenyl)-4H-benzo-[1,3]-oxazine-4-one (6).In step 4, the 6,8-(un/mono/di)-bromo-2-(methyl/phenyl)-4H-benzo-[1,3]-oxazine-4-ones (6) were allowed to react with 2-amino-4-phenyl thiazole (2) / 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo-thiophene (4) in dry pyridine to yield the title compounds (7a-l). Structural elucidation of synthesized compounds was attained by the aid of IR, ^{1}H-NMR, mass spectral and elemental analysis. All the title compounds were screened for anti-oxidant activities.

Synthesis of 2-amino-4-phenyl thiazole (2):

A mixture consisting of acetophenone (1) (0.1 mol) and thiourea (0.2 mol), add bromine (0.2 mol) drop wise very slowly. After the addition of bromine, the reaction mixture was heated on water bath for overnight, and water was added to it and again heated until most of the solid has gone into solution. The reaction mixture was filtered when it is hot and the filtrate was cooled. It was made alkaline with conc. ammonium hydroxide to separate 2-amino-4-phenyl thiazole[18]. The product was filtered, washed with alcohol and dried over phosphorous pentoxide. It was recrystallised from ethanol, as colorless needles (2). Yield (84.2%), m.p. 120-122^{0}C.

Synthesis of 2-amino-3-carbethoxy-4,5,6,7-tetrahydro benzo-thiophene (4):

To a mixture of cyclohexanone (3) (0.2 mol), ethylcyanoacetate (0.2 mol) and sulphur (0.2 mol) in ethanol (40 ml), diethylamine (0.2 mol) was added drop wise with stirring. The 2-amino-3-carbethoxy-4,5,6,7-tetrahydro benzothiophene[19] crystals (4) obtained are filtered and recrystallized from ethanol. Yield (89.5%), m.p. 119-121^{0}C.



Scheme 1: Synthesis of novel Quinazolinone (7a-7l)

Synthesis of 6,8-(un/mono/di)-bromo-2–(methyl/phenyl)-4H-benzo-(1,3)-oxazin–4-one (6)

For the synthesis of 2-methyl derivative a mixture of 3,5-(un/mono/di)-bromo anthranilic acid (5a-c) (0.01mol) and acetic anhydride (0.1mol) was refluxed on gentle flame for 4 h. The excess of acetic anhydride was distilled off under reduced pressure and the residue was dissolved in petroleum ether and kept aside for1h. The light brown solid (6a-c) which obtained was filtered and dried.

For the synthesis of 2-phenyl derivative to a solution of 3,5-(un/mono/di)-bromo anthranilic acid (5a-c) (0.1 mol) dissolved in pyridine (60 ml), benzoyl chloride (0.2 mol) was added. The mixture was stirred for 30 min followed by treatment with 5% $NaHCO_3$ (15 ml). The solid (6d-f) obtained was recrystallized from ethanol.

Synthesis of title compounds (7a-l)

A mixture of **6a-f** (0.02 mol) and 2/4 (0.01 mol) in dry pyridine (80 mL) was refluxed for overnight. After refluxing, the excess of solvent was removed and the residue was neutralized with hydrochloric acid. The solid separated out was washed with water and recrystallised from ethanol to yield title compounds (7a-l). The physical data of the title compounds are depicted in Table 1.

Anti-oxidant screening (DPPH radical scavenging activity)

DPPH solution[20], 1 mmol/L, was prepared by dissolving 31.54 mg DPPH in 95% v/v buffered methanol (40 mL of 0.1 mol/L acetate buffer (pH 5.5) with 60 mL of methanol) and made up to 50 mL with buffered methanol. The synthesized compounds (7a-l) at different concentrations such as 0.2, 0.4, 0.6, 0.8, 1.0 mL (200, 400, 600, 800 and 1000 µg/ mL) were made up to 4 mL with distilled water. 1 mL of DPPH (1 mmol, 3.953×10^{-10} µg/ mL) was added to each test tube, shaken and the reaction mixture was kept at 30^0 C for 30 minutes. Absorbance of the resulting solution was measured spectrophotometrically at 517 nm. The effect of ascorbic acid (vitamin C) on DPPH was also assessed for comparison with that of synthesized compounds (7a-l). A buffered methanolic dilution (0.2, 0.4, 0.6, 0.8, 1.0 mL) of 1 mg/ mL ascorbic acid was made to 4 mL with distilled water. 1 mL DPPH radical (1mmol/L) was added to each tube and same procedure as in DPPH scavenging experiment was followed. The absorbance measured for the control solution[21] (Buffered methanol with DPPH) was in the range 0.500 ± 0.040. Anti-radical activity was expressed as inhibition percentage (I %) and calculated using the following equation.

Inhibition Percentage = [(Absorbance control – Absorbance sample)/Absorbance control] × 100

RESULTS AND DISCUSSION

Chemistry

IR, ^{1}H-NMR, Mass spectra and Elemental analysis were consistent with the assigned structures.

2-Methyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one [7a]. IR (KBr, cm^{-1}): 3017 (Ar-CH), 2915 (CH in CH_3), 1720 (C=O), 1518 (C=N), 1462 (C=C), 653 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 7.20-7.85 (m, 9H; C_5,C_6,C_7,C_8,$C_{2''}$,$C_{3''}$,$C_{4''}$,$C_{5''}$,$C_{6''}$; Ar-H), 6.71 (s, 1H; $C_{5'}$), 0.87 (s, 3H; C_2, -C<u>H</u>$_3$). EI-MS *(m/z)*: 319 (Calcd for $C_{18}H_{13}N_3OS$; 319.38). Anal. Calcd for $C_{18}H_{13}N_3OS$: C, 67.69; H, 4.10; N, 13.16. Found: C, 67.60; H, 4.07; N, 13.11.

6-Bromo-2-methyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one [7b]. IR (KBr, cm^{-1}): 3041 (Ar-CH), 2920 (CH in CH_3), 1725 (C=O), 1514 (C=N), 1457 (C=C), 646 (C-S), 568 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.18-8.07 (m, 8H; C_5,C_7,C_8, $C_{2''}$,$C_{3''}$,$C_{4''}$,$C_{5''}$,$C_{6''}$; Ar-H), 6.58 (s, 1H; $C_{5'}$), 0.89 (s, 3H; C_2, -C<u>H</u>$_3$). EI-MS *(m+2)*: 400 (Calcd for $C_{18}H_{12}BrN_3OS$; 398.28). Anal. Calcd for $C_{18}H_{12}BrN_3OS$: C, 54.28; H, 3.04; N, 10.55. Found: C, 54.21; H, 3.00; N, 10.49.

6,8-Dibromo-2-methyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one [7c]. IR (KBr, cm^{-1}): 3032 (Ar-CH), 2926 (CH in CH_3), 1764 (C=O), 1522 (C=N), 1453 (C=C), 666 (C-S), 583 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.05-7.99 (m, 7H; C_5,C_7,$C_{2''}$,$C_{3''}$,$C_{4''}$,$C_{5''}$,$C_{6''}$; Ar-H), 6.65 (s, 1H; $C_{5'}$), 0.95 (s, 3H; C_2, -C<u>H</u>$_3$). EI-MS *(m+2)*: 479 (Calcd for $C_{18}H_{11}Br_2N_3OS$; 477.17). Anal. Calcd for $C_{18}H_{11}Br_2N_3OS$: C, 45.31; H, 2.32; N, 8.81. Found: C, 45.22; H, 2.26; N, 8.77.

2-Methyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one [7d]. IR (KBr, cm^{-1}): 3040 (Ar-CH), 2935 (CH in CH_3), 1722 (C=O), 1519 (C=N), 1448 (C=C), 669 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 7.53-8.05 (m, 4H; C_5,C_6,C_7,C_8; Ar-H), 4.37 (tet, 2H; -C<u>H</u>$_2$), 1.57-2.67 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.45 (tri, 3H; -C<u>H</u>$_3$), 0.84 (s, 3H; -C<u>H</u>$_3$). EI-MS *(m/z)*: 368 (Calcd for $C_{20}H_{20}N_2O_3S$; 368.45). Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60. Found: C, 65.13; H, 5.42; N, 7.55.

6-Bromo-2-methyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one [7e]. IR (KBr, cm^{-1}): 3018 (Ar-CH), 2912 (CH in CH_3), 1724 (C=O), 1532 (C=N), 1463 (C=C), 651 (C-S), 574 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.47-7.99 (m, 3H; C_5,C_7,C_8; Ar-H), 4.33 (tet, 2H; -C<u>H</u>$_2$), 1.53-2.60 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.39 (tri, 3H; -C<u>H</u>$_3$), 0.87 (s, 3H; -C<u>H</u>$_3$). EI-MS *(m+2)*: 449 (Calcd for $C_{20}H_{19}BrN_2O_3S$; 447.35). Anal. Calcd for $C_{20}H_{19}BrN_2O_3S$: C, 53.70; H, 4.28; N, 6.26. Found: C, 53.61; H, 4.26; N, 6.19.

6,8-Dibromo-2-methyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one [7f]. IR (KBr, cm^{-1}): 3046 (Ar-CH), 2920 (CH in CH_3), 1715 (C=O), 1524 (C=N), 1450 (C=C), 643 (C-S), 580 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.69-8.06 (m, 2H; C_5,C_7; Ar-H), 4.26 (tet, 2H; -C<u>H</u>$_2$), 1.59-2.61 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.35 (tri, 3H; -C<u>H</u>$_3$), 0.89 (s, 3H; -C<u>H</u>$_3$). EI-MS *(m+2)*: 528 (Calcd for $C_{20}H_{18}Br_2N_2O_3S$; 526.24). Anal. Calcd for $C_{20}H_{18}Br_2N_2O_3S$: C, 45.65; H, 3.45; N, 5.32. Found: C, 45.61; H, 3.39; N, 5.28.

2-Phenyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one [7g]. IR (KBr, cm^{-1}): 3048 (Ar-CH), 2932 (CH in CH_3), 1726 (C=O), 1513 (C=N), 1446 (C=C), 655 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 7.11-8.13 (m, 14H; C_5,C_6,C_7,C_8,$C_{2'''}$,$C_{3''}$,$C_{4''}$,$C_{5''}$, $C_{6''}$,$C_{2'''}$,$C_{3'''}$,$C_{4'''}$,$C_{5'''}$,$C_{6'''}$; Ar-H), 6.68 (s, 1H; $C_{5'}$). EI-MS *(m/z)*: 381 (Calcd for $C_{23}H_{15}N_3OS$; 381.45). Anal. Calcd for $C_{23}H_{15}N_3OS$: C, 72.42; H, 3.96; N, 11.02. Found: C, 72.39; H, 3.89; N, 10.99.

6-Bromo-2-phenyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one [7h]. IR (KBr, cm^{-1}): 3036 (Ar-CH), 2926 (CH in CH_3), 1722 (C=O), 1520 (C=N), 1460 (C=C), 647 (C-S), 564 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.09-8.01 (m, 13H; C_5,C_7,C_8,$C_{2''}$, $C_{3''}$,$C_{4''}$,$C_{5''}$,$C_{6''}$,$C_{2'''}$,$C_{3'''}$,$C_{4'''}$,$C_{5'''}$,$C_{6'''}$; Ar-H), 6.61 (s, 1H; $C_{5'}$). EI-MS *(m+2)*: 462 (Calcd for $C_{23}H_{14}BrN_3OS$; 460.35). Anal. Calcd for $C_{23}H_{14}BrN_3OS$: C, 60.01; H, 3.07; N, 9.13. Found: C, 59.91; H, 3.02; N, 9.09.

6,8-Dibromo-2-phenyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one [7i]. IR (KBr, cm^{-1}): 3024 (Ar-CH), 2939 (CH in CH_3), 1720 (C=O), 1526 (C=N), 1452 (C=C), 670 (C-S), 577 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.29-8.22 (m, 12H; C_5,C_7,$C_{2''}$,$C_{3''}$, $C_{4''}$,$C_{5''}$,$C_{6''}$,$C_{2'''}$,$C_{3'''}$,$C_{4'''}$,$C_{5'''}$,$C_{6'''}$; Ar-H), 6.73 (s, 1H; $C_{5'}$). EI-MS *(m+2)*: 541 (Calcd for $C_{23}H_{13}Br_2N_3OS$; 539.24). Anal. Calcd for $C_{23}H_{13}Br_2N_3OS$: C, 51.23; H, 2.43; N, 7.79. Found: C, 51.17; H, 2.41; N, 7.75.

2-Phenyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one [7j]. IR (KBr, cm^{-1}): 3032 (Ar-CH), 2922 (CH in CH_3), 1718 (C=O), 1514 (C=N), 1455 (C=C), 665 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 7.21-7.97 (m, 9H; C_5,C_6,C_7,C_8,$C_{2''}$,$C_{3''}$,$C_{4''}$,$C_{5''}$, $C_{6''}$; Ar-H), 4.34 (tet, 2H; -C<u>H</u>$_2$), 1.60-2.58 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.37 (tri, 3H; -C<u>H</u>$_3$). EI-MS *(m/z)*: 430 (Calcd for $C_{25}H_{22}N_2O_3S$; 430.52). Anal. Calcd for $C_{25}H_{22}N_2O_3S$: C, 69.75; H, 5.15; N, 6.51. Found: C, 69.71; H, 5.12; N, 6.42.

6-Bromo-2-phenyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one [7k]. IR (KBr, cm^{-1}): 3019 (Ar-CH), 2917 (CH in CH_3), 1726 (C=O), 1518 (C=N), 1454 (C=C), 649 (C-S), 561 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.27-8.05 (m, 8H; C_5,C_7,C_8,$C_{2''}$,$C_{3''}$, $C_{4''}$,$C_{5''}$,$C_{6''}$; Ar-H), 4.31 (tet, 2H; -C<u>H</u>$_2$), 1.58-2.62 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.39 (tri, 3H; -C<u>H</u>$_3$). EI-MS *(m+2)*: 511 (Calcd for $C_{25}H_{21}BrN_2O_3S$; 509.41). Anal. Calcd for $C_{25}H_{21}BrN_2O_3S$: C, 58.94; H, 4.16; N, 5.50. Found: C, 58.90; H, 4.11; N, 5.47.

6,8-Dibromo-2-phenyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one [7l]. IR (KBr, cm^{-1}): 3041 (Ar-CH), 2924 (CH in CH_3), 1715 (C=O), 1524 (C=N), 1450 (C=C), 663 (C-S), 573 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.34-8.17 (m, 7H; C_5,C_7,$C_{2''}$,$C_{3''}$,$C_{4''}$, $C_{5''}$,$C_{6''}$; Ar-H), 4.26 (tet, 2H; -C<u>H</u>$_2$), 1.53-2.61 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.36 (tri, 3H; -C<u>H</u>$_3$). EI-MS *(m+2)*: 590 (Calcd for $C_{25}H_{20}Br_2N_2O_3S$; 588.31). Anal. Calcd for $C_{25}H_{20}Br_2N_2O_3S$: C, 51.04; H, 3.43; N, 4.76. Found: C, 51.01; H, 3.40; N, 4.72.

Table 1: Formula and physical constants of compounds 7a-7l

Comp	X	X_1	R	R_1	Mol. formula	M.W	m.p (^{0}C)	Yield (%)
7a	H	H	CH_3	C_9H_6NS	$C_{18}H_{13}N_3OS$	319	160-162	85
7b	Br	H	CH_3	C_9H_6NS	$C_{18}H_{12}BrN_3OS$	398	272-275	79
7c	Br	Br	CH_3	C_9H_6NS	$C_{18}H_{11}Br_2N_3OS$	477	221-223	77
7d	H	H	CH_3	$C_{11}H_{13}O_2S$	$C_{20}H_{20}N_2O_3S$	368	109-110	81
7e	Br	H	CH_3	$C_{11}H_{13}O_2S$	$C_{20}H_{19}BrN_2O_3S$	447	91-93	76
7f	Br	Br	CH_3	$C_{11}H_{13}O_2S$	$C_{20}H_{18}Br_2N_2O_3S$	526	64-66	74
7g	H	H	C_6H_5	C_9H_6NS	$C_{23}H_{15}N_3OS$	381	79-82	69
7h	Br	H	C_6H_5	C_9H_6NS	$C_{23}H_{14}BrN_3OS$	460	194-196	66
7i	Br	Br	C_6H_5	C_9H_6NS	$C_{23}H_{13}Br_2N_3OS$	539	105-107	65
7j	H	H	C_6H_5	$C_{11}H_{13}O_2S$	$C_{25}H_{22}N_2O_3S$	430	83-85	67
7k	Br	H	C_6H_5	$C_{11}H_{13}O_2S$	$C_{25}H_{21}BrN_2O_3S$	509	139-141	61
7l	Br	Br	C_6H_5	$C_{11}H_{13}O_2S$	$C_{25}H_{20}Br_2N_2O_3S$	588	112-114	64

Anti-oxidant screening (DPPH radical scavenging activity)

The results of anti-oxidant screening were depicted in Table 2. DPPH radical scavenging is considered a good *in vitro* model and is widely used to conveniently assess antioxidant efficacy. In its radical form, DPPH has an absorbance at 515 nm which disappears when DPPH is reduced by an antioxidant compound or a radical species to become a stable diamagnetic molecule. As a result, the color changes from

purple to yellow. This color change is taken as an indication of the hydrogen donating ability of the tested compounds.

Antioxidants can react with DPPH and produce 1,1-diphenyl-2-picryl-hydrazine. The reducing abilities of the examined compounds were determined by their interaction with the free stable radical 1,-1-diphenyl-2-picryl-hydrazine (DPPH) at five different concentrations for 30 min. The highest scavenger activity observed in compound 7i is probably due to the presence of bromo groups at positions 6, 8, phenyl group at 2nd position and thiazole nucleus at 3rd position of qiunazolin-4(3H)-one ring. Generally electron withdrawing substituents deactivate aromatic ring and have no capability to bind the free radicals. From the results, brominated compound exhibited better activity than unsubstituted one and phenyl derivatives exhibited more activity than methyl derivative. In addition to that, thiazole derivatives exhibited more activity than the corresponding tetra hydro benzothiophene.

Table 2: Anti-radical activity of compounds 7a-7l (expressed as % inhibition)

Compounds	Concentration of drugs (in µg/mL)				
	200	**400**	**600**	**800**	**1000**
7a	11	16	18	30	36
7b	17	25	32	46	48
7c	24	31	42	53	60
7d	8	14	18	26	33
7e	18	22	29	41	44
7f	23	30	41	52	58
7g	15	20	24	38	40
7h	20	28	37	49	55
7i	31	43	50	62	73
7j	14	17	20	33	37
7k	19	26	35	45	51
7l	26	34	47	55	67
Vitamin-C	42	56	63	79	98

CONCLUSION

Several new quinazolin-4(3H)-ones were synthesized in moderate to good yield. The antioxidant properties of these molecules were evaluated by DPPH radical scavenging activity method. The prominent antioxidant effectiveness of the studied compounds seems to be related to the presence of bromine, phenyl ring and thiazole nucleus in the quinazolin-4(3H)-one ring. In the future, further studies with different substituent will be performed.

REFERENCES

1. Alagarsamy V, Rajasolomon V, Meena R and Ramseshu KV. Synthesis, analgesic, anti-inflammatory and anti-bacterial activities of some novel 2-butyl 3-substituted quinazolin-4(3H)-ones. Biol. Pharm. Bull., 2005; 28(6): 1091-1094.
2. Kant P. Synthesis and anti-microbial activities of some new 2-substituted 3(1'-aryl-4'-nitrophenyl imidazol-5'-yl) amino quinazolin-4-ones. Indian J. Heterocycl. Chem., 2006; 15: 221-224.
3. El-Hiti GA, Abdel-Megeed MF and Zied TMM. Synthesis and reaction of some 3-aryl 2-thioxo quinazolin-4(3H)-ones. Indian J. Chem., 2002; 41B: 1519-1522.
4. Alagarsamy V, Thangathirupathi A, Mandal SC, Rajasekaran S, Vijayakumar S, Revathi R, Anburaj J, Arunkumar S and Rajesh S. Pharmacological evaluation of 2-substituted (1,3,4)-thiadiazolo quinazolines. Indian J. Pharm. Sci., 2006; 68(1): 108-111.
5. Nandy P, Vishalakshi MT and Bhat AR. Synthesis and antitubercular activity of mannich bases of 2-methyl 3H-quinazolin-4-ones. Indian J. Heterocycl. Chem., 2006; 15: 293-294.
6. Mahajan NS, Pattan SR, Jadhav RL, Pimpodkar NV and Manikrao AM. Synthesis of some thiazole compounds of biological interest containing mercapto group. Int. J. Chem. Sci., 2008; 6(2): 800-806.
7. Srivastava SD and Sen JP. Synthesis of biological evaluation of 2-aminibenzothiazole derivatives. Indian J. Chem., 2008; 47B: 1583-1586.
8. Chowki AA, Magdum CS, Ladda PL and Mohite SK. Synthesis and antitubercular activity of 6-nitro-2-[4-formyl-3-(substituted phenyl) pyrazol-1-yl] benzothiazoles. Int. J. Chem. Sci., 2008; 6(3): 1600-1605.
9. Souren A, Jack M and Gustav JM. Synthesis and microbiological properties of (2-benzothienyl) aminopropionic acid. J. Am. Chem., 1948; 70(9): 3075-3076.
10. Kristina S, Marijeta K, Ivo P, Lidija S, Kresimir P and Grace KZ. Synthesis, photochemical synthesis, DNA binding and antitumor evaluation of novel cyano- and amidino-substituted derivatives of naphtha-furans, naptho-thiophenes, thieno-benzofurans, benzo-thiophenes and their acyclic precursors. Eur. J. Med. Chem., 2006; 41: 925-939.
11. Krzysztof K, Yijun Z, Damon P, Jeffrey D, Peter PR and Vinay KP. New HIV-1 reverse transcriptase inhibitors based on a tricyclic benzothiophene scaffold: Synthesis, resolution, and inhibitory activity. Bioorganic and Med. Chem., 2006; 16: 3034-3038.
12. Finkel T and Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature, 2000; 408: 239–247.
13. Devasagayam TPA, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS and Lele RD. Free radicals and antioxidants in human health: current status and future prospects. J.Assoc.Phys. India. 2004; 52: 794–804.
14. Miller AL. Antioxidant flavonoids: Structure, function and clinical usage. Alt. Med.Rev., 1996; 1: 103–111.
15. Rajasekaran S, GopalKrishna R, Sanjay Pai PN and Gurpreet Singh S. Synthesis, Antibacterial and invitro Antioxidant Activity2,3-Substituted Quinazolin-4(3H)-ones. J. Chem. Pharm. Res., 2010; 2(1): 482-488.
16. Geronikaki A, Hadjipavlou-Litina D, Chatziopoulos C and Soloupis G. Synthesis and Biological Evaluation of New 4,5-Disubstituted-Thiazolyl Amides, Derivatives of 4-Hydroxy-Piperidine or of 4-N-Methyl Piperazine. Molecules, 2003; 8: 472-479.
17. Isabel CFR Ferreira, Maria-Joao RP Queiroz, Miguel VB, Leticia ME, Agathe B and Gilbert K. Evaluation of the antioxidant properties of diarylamines in the benzo[b]thiophene series by free radical scavenging activity and reducing power. Bioorg. Med. Chem. Lett., 2006; 16: 1384–1387.
18. Pattan SR, Shamrez Ali M, Pattan JS, Purohit SS, Reddy VVK and Nataraj BR. Synthesis and microbiological evaluation of 2-acetanilido-4-aryl thiazole derivatives. Indian J. Chem., 2006; 45B: 1929-1932.
19. Jyothi C, Kumar Das A, Pal P and Baidya M. Synthesis and anti-inflammatory activities of some new substituted thiadiazolothieno-pyrimidinones. Indian J. Heterocycl. Chem., 2007; 17: 191-192.
20. Hatano T, Kagawa H, Yasuhara T and Okuda T. Two new flavonoids and other constituents in licorice roots: their relative astringency and radial scavenging effects. Chemical and Pharmarcological Bulletin, 1988; 36: 2090-2097.
21. Sharma OP and Bhat TK. DPPH antioxidant assay revisited. Food Chemistry, 2009; 113: 1202-1205.