

SYNTHESIS, ANTIOXIDANT AND ANTICANCER ACTIVITY OF NEW QUINOLINE-[1, 2, 4]-TRIAZOLE HYBRIDS

Hemant Hegde¹, Santosh L. Gaonkar¹, Naveen P. Badiger²
and Nitinkumar S. Shetty^{1*}

¹Department of Chemistry, Manipal Institute of Technology, Manipal Academy of Higher Education, Manipal-576104, (Karnataka) India

²P.G. Dept. of Chemistry, JSS College, Vidyagiri, Dharwad-580004, (Karnataka) India

*E-mail: nitin.shetty@manipal.edu

ABSTRACT

A set of quinoline coupled triazole derivatives was synthesized using substituted quinoline hydrazide and isothiocyanate derivatives. The structures of the synthesized molecules were confirmed using spectral techniques like FTIR, ¹H & ¹³C NMR spectroscopy. Novel triazole thione derivatives were subjected to anticancer and antioxidant activity. The studies revealed the moderate anticancer activity of the molecules but have shown potent antioxidant activity.

Keywords: Quinoline-[1, 2, 4]-triazole, Molecular Hybrids, Anticancer Activity, Antioxidant Activity.

© RASAYAN. All rights reserved

INTRODUCTION

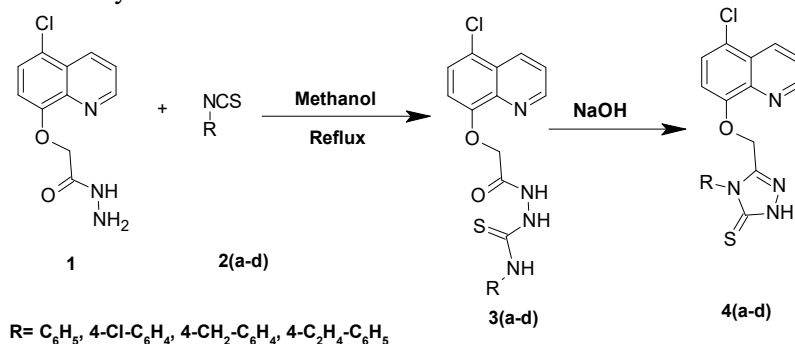
The 1, 2, 4-triazoles are the vital units of an exigent class of heterocycles. They offer outstretched pharmacological benefits as antimicrobial, anticancer, antioxidant and several other applications.¹⁻³ In the recent progress in medicinal chemistry, the synthesis of various 3-mercapto-1, 2, 4- triazole derivatives have gathered a considerable attraction owing to their significance in the field of medicinal chemistry.⁴⁻⁸ The biological activities exhibited by the 3-mercapto-1, 2, 4- triazoles is found to be because of the presence of =N-C-S moiety.⁹

On the other hand, quinolines are another important heterocyclic member that grabbed the attention of many researchers owing to its wide spectrum of pharmaceutical application.¹⁰⁻¹³ In the present work, 5-chloro-8-hydroxy quinoline is derivatized which is an analog of a clioquinol (a broad-spectrum antibacterial and antifungal agent). Structural modification of the basic skeleton would help in the identification of new lead molecules to fight against life-threatening diseases like cancer.¹⁴ Not much work has been done on the development of 1, 2, 4-triazole-quinoline hybrid. Shaker¹⁵ reviewed the most important procedures for the synthesis of 3-mercapto-1, 2, 4- triazoles. It is reported that the 3-mercapto-1, 2, 4- triazole has proved to be a rich source of various heterocyclic compounds. Fascinated by the biological profiles of triazoles and quinolines, we have designed and synthesized a new series of hybrid molecules that would produce a synergistic effect which also helps in the development of potential therapeutic agents. Recent findings reported that the antioxidants help in reducing the metastasis by reducing reactive oxygen species in cancer cells.¹⁶ This prompted us to test the newly synthesized compounds for their *in vitro* anticancer and antioxidant activity.

EXPERIMENTAL

Chemicals were purchased commercially and were used as such without any purification. The reaction progress was monitored with the help of Thin-layer chromatography (TLC). Aluminum sheets precoated with alichrosep silica gel-60/UV₂₅₄ was used as a stationary phase with iodine and UV light as visualizing agents. The melting point was checked using Thiele's tube in an open capillary tube. Functional group identification was done by FTIR spectra which were recorded on Shimadzu Infrared spectrometer (8400s)

using KBr as background. ^1H and ^{13}C NMR spectra were recorded on Bruker NMR-400 MHz and 100 MHz respectively with TMS as an internal standard. Elemental analysis was performed by using Perkin Elmer (2400) CHN elemental analyzer.



Scheme-1: Synthesis of Quinoliny Triazole Hybrids

Synthesis of Quinoline Hydrazone Derivative, (1)

5-Chloro-quinolin-8-yloxy-acetohydrazide (**1**) was prepared by reacting corresponding esters (1 mmol) with hydrazine hydrate, 99 % (1.5 mmol) in ethanol (2 mL). Solid thus formed was filtered, dried, and used directly for the next step without further purification (recrystallization).^{17,18}

2-[(5-chloroquinolin-8-yl)oxy]acetohydrazide (**1**)

Yield, 95 %, m. p. 118-120 °C; FTIR (KBr): $\nu_{\text{max}} = 3319$ (N-H), 3041 (Ar-H), 2936 (CH_2), 1672 ($\text{C}=\text{O}$), 1616 ($\text{C}=\text{N}$), 1506 ($\text{C}=\text{C}$), 777 (Ar-C-Cl) cm^{-1} . ^1H NMR (400MHz, DMSO-d_6) δ : 8.87 (d, 1H, $J = 3.4$ Hz, quinoline ring-H), 8.14 (d, 1H, $J = 8.4$ Hz, quinoline ring-H), 7.68-6.84 (m, 11H, Ar-H), 4.76 (s, 2H, OCH_2), 4.39 (s, 2H, N-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 68.4, 111.8, 122.2, 123.6, 126.7, 127.2, 132.8, 140.8, 150.5, 153.8, 166.9 ppm. Elemental analysis, Anal. calcd. for $\text{C}_{11}\text{H}_{10}\text{ClN}_3\text{O}_2$: C, 52.47; H, 3.96; N, 16.74. Found: C, 52.50; H, 4.01; N, 16.70 %.¹⁸

Synthesis of Quinoliny Carbothioamide 3(a-d)

An equimolar mixture of quinoline hydrazide **1** (2 mmol) and aryl-substituted isothiocyanate, **2(a-d)** was refluxed in methanol (5 mL). On completion of the reaction (as confirmed by TLC), reaction content was cooled and filtered the solid thus formed. The crude product was recrystallized by using methanol to afford pure quinoliny carbothioamide **3(a-d)**.

2-(2-((5-chloroquinolin-8-yl)oxy)acetyl)-N-phenylhydrazine-1-carbothioamide, (3a)

Yield, 91 %, m. p. 146-148 °C; FTIR (KBr): $\nu_{\text{max}} = 3319, 3025, 1682, 1552, 1309, 1238, 781$ cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6) δ : 10.28 (1H, s, NH), 9.76 (1H, s, NH), 9.64 (1H, s, NH), 9-9.02 (d, 1H, $J = 4$ Hz, Quinoline ring H), 8.54-8.56 (d, 1H, $J = 8$ Hz, Quinoline ring-H), 7.71-7.78 (2H, d, Quinoline ring-H, $J = 8$ Hz), 7.67-7.69 (2H, d, Quinoline ring-H, $J = 12$ Hz), 7.38-7.42 (1H, m, Quinoline ring-H), 7.30-7.34 (3H, m, Ar-H), 4.86 (2H, s, CH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ : 66.7, 113.1, 117.3, 120.5, 122.9, 123.4, 125.8, 126.2, 130.4, 136.7, 142.7, 151.7, 155.3 ppm; Anal. Calcd. for $\text{C}_{18}\text{H}_{15}\text{ClN}_4\text{O}_2\text{S}$: C, 55.89; H, 3.91; N, 14.48. Found: C, 56.02; H, 3.95; N, 14.44.

N-(4-Chlorophenyl)-2-(2-((5-chloroquinolin-8-yl)oxy)acetyl)hydrazine-1-carbothioamide, (3b)

Yield, 87 %, m. p. 152-153 °C; FTIR (KBr): $\nu_{\text{max}} = 3209, 3021, 1689, 1533, 1311, 1240, 783$ cm^{-1} ; ^1H NMR (400 MHz, DMSO-d_6) δ : 10.40 (1H, s, NH), 9.83 (1H, s, NH), 9.81 (1H, s, NH), 9.0-9.01 (d, 1H, $J = 4$ Hz, Quinoline ring H), 8.54-8.56 (d, 1H, $J = 8$ Hz, Quinoline ring-H), 7.71-7.77 (2H, d, Quinoline ring-H, $J = 8$ Hz), 7.47-7.49 (2H, d, Quinoline ring-H, $J = 12$ Hz), 7.40-7.43 (1H, m, Quinoline ring-H), 7.28-7.30 (2H, d, Ar-H, $J = 8$ Hz), 4.93 (2H, s, CH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ : 68.04, 113.9, 117.6,

120.4, 125.1, 126.6, 128.2, 130.2, 137.1, 142.6, 151.5, 154.8, 162.5, 163.5, 166.0 ppm; Anal. Calcd. for $C_{18}H_{14}Cl_2N_4O_2S$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.29; H, 3.36; N, 13.27.

N-Benzyl-2-(2-((5-chloroquinolin-8-yl)oxy)acetyl)hydrazine-1-carbothioamide, (3c)

Yield, 82 %, m. p. 150-152 °C; FTIR (KBr): ν_{\max} = 3209, 3021, 1689, 1533, 1311, 1240, 783 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6), δ : 10.40 (1H, s, NH), 9.83 (1H, s, NH), 9.81 (1H, s, NH), 9.0-9.01 (d, 1H, J = 4 Hz, Quinoline ring H), 8.54-8.56 (d, 1H, J = 8 Hz, Quinoline ring-H), 7.71-7.77 (2H, d, Quinoline ring-H, J = 8 Hz), 7.47-7.49 (2H, d, Quinoline ring-H, J = 12 Hz), 7.40-7.43 (1H, m, Quinoline ring-H), 7.28-7.30 (2H, d, Ar-H, J = 8 Hz), 4.93 (2H, s, CH_2) ppm; ^{13}C NMR (100 MHz, DMSO- d_6), δ : 35.41, 68.01, 112.3, 113.1, 123.4, 126.3, 126.8, 127.3, 129.1, 129.7, 132.6, 139.6, 140.9, 150.6, 154.2 ppm; Anal. Calcd. for $C_{19}H_{17}ClN_4O_2S$: C, 56.93; H, 4.27; N, 13.98. Found: C, 57.01; H, 4.32; N, 14.06.

2-(2-((5-Chloroquinolin-8-yl)oxy)acetyl)-N-phenethylhydrazine-1-carbothioamide, (3d)

Yield, 95 %, m. p. 148-150 °C; FTIR (KBr): ν_{\max} = 3228, 1681, 1556, 1504, 1311, 783 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6), δ : 9.0 (1H, s, NH), 8.54-8.56 (d, 1H, J = 8 Hz, Quinoline ring-H), 8.19 (1H, s, NH), 7.71-7.77 (2H, d, Quinoline ring-H, J = 8 Hz), 7.47-7.49 (2H, d, Ar-H, J = 12 Hz), 7.40-7.43 (1H, m, Quinoline ring-H), 7.19-7.32 (8H, m, Ar-H), 4.89 (2H, s, CH_2), 3.62-3.67 (2H, s, CH_2), 2.80-2.84 (2H, m, CH_2) ppm; ^{13}C NMR (100 MHz, DMSO- d_6), δ : 35.35, 40.06, 68.0, 112.3, 112.9, 123.6, 126.6, 126.7, 127.1, 128.8, 129.0, 132.8, 139.6, 140.7, 150.5, 153.8 ppm; Anal. Calcd. for $C_{20}H_{19}ClN_4O_2S$: C, 57.90; H, 4.62; N, 13.50. Found: C, 57.98; H, 4.59; N, 13.38.

Synthesis of Quinolinyl Triazole 4(a-d)

Quinoline carbothioamide **3(a-d)** (1 mmol) with 5 % NaOH (aqueous) at 70°C for 1h to form the titled compounds **4(a-d)**. Progress of the reaction was monitored by using thin-layer chromatography by taking toluene: ethyl acetate; 2:1 respectively as mobile phase. Cooled and acidified with 6N HCl and crystallized from ethanol to afford pure quinolinyl triazole derivatives **4(a-d)**. The crude product was recrystallized using methanol.

5-(((5-Chloroquinolin-8-yl)oxy)methyl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (4a)

Yield: 78 %, m.p. 218-220 °C, FTIR (KBr): ν_{\max} = 3436, 3045, 1612, 1589, 1467, 783 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6), δ : 14.09 (s, 1H, -NH), 8.54-9.01 (m, 2H, quinoline-H), 8.50-8.51 (d, 1H, quinoline-H, J = 4 Hz), 7.76-7.77 (d, 1H, quinoline-H, J = 4 Hz), 7.22-7.75 (m, 5H, Ar-H), 5.22 (s, 2H, O- CH_2) ppm; ^{13}C -NMR (100 MHz, DMSO- d_6) δ : 61.91, 112.4, 115.8, 116.3, 123.5, 123.9, 126.8, 130.3, 130.8, 131.5, 133.0, 140.8, 148.3, 150.9, 153.2, 161.4, 163.9, 169.4 ppm; Anal. Calcd for $C_{18}H_{13}ClN_4OS$: C, 58.62; H, 3.55; N, 15.19. Found: C, 58.58; H, 3.62; N, 15.24.

4-(4-Chlorophenyl)-5-(((5-chloroquinolin-8-yl)oxy)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione(4b)

Yield: 87 %, m. p. 237-238 °C, FTIR (KBr): ν_{\max} = 3436, 3045, 1612, 1589, 1467, 783 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6), δ : 14.13 (s, 1H, -NH), 8.51-8.97 (m, 2H, quinoline-H), 8.49-8.5 (d, 1H, quinoline-H, J = 1.6Hz), 7.72-7.73 (d, 1H, quinoline-H, J = 4Hz), 7.20-7.67 (m, 4H, Ar-H), 5.22 (s, 2H, O- CH_2) ppm; ^{13}C -NMR (100 MHz, DMSO- d_6) δ : 61.96, 112.6, 116.2, 116.5, 123.3, 123.6, 127.1, 129.9, 131.0, 131.1, 132.8, 140.7, 148.4, 150.6, 152.7, 161.3, 163.7, 169.2 ppm; Anal. Calcd for $C_{18}H_{12}Cl_2N_4OS$ (%): C 53.61, H 3.0, N 13.89; Found: C 53.58, H 2.92, N 14.01.

4-Benzyl-5-(((5-chloroquinolin-8-yl)oxy)methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (4c)

Yield: 71 %, m. p. 230-232 °C, FTIR (KBr): ν_{\max} = 3428, 3052, 1609, 1593, 1462, 785 cm^{-1} ; 1H NMR (400 MHz, DMSO- d_6), δ : 14.09 (s, 1H, -NH), 8.55-8.94 (m, 2H, quinoline-H), 8.53-8.54 (d, 1H, quinoline-H, J = 1.6 Hz), 7.75-7.76 (d, 1H, quinoline-H, J = 4 Hz), 7.23-7.71 (m, 4H, Ar-H), 5.23 (s, 2H, O- CH_2) ppm; ^{13}C -NMR (100 MHz, DMSO- d_6) δ : 61.8, 112.4, 116.2, 116.5, 123.3, 123.6, 127.1, 129.9, 131.0, 131.1, 132.8, 140.7, 148.4, 150.6, 152.7, 161.3, 163.7, 169.2 ppm; Anal. Calcd for $C_{18}H_{12}Cl_2N_4OS$ (%): C 53.61, H 3.0, N 13.89; Found: C 53.58, H 3.05, N 13.95

5-(((5-Chloroquinolin-8-yl)oxy)methyl)-4-phenethyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (4d)

Yield: 73 %, m. p. 224-226 °C, FTIR (KBr): ν_{\max} = 3432, 3054, 1616, 1591, 1462, 788 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6) δ : 14.11 (s, 1H, -NH), 8.50-9.01 (m, 2H, quinoline-H), 8.51-8.514 (d, 1H, quinoline-H, J = 1.6 Hz), 7.69-7.70 (d, 1H, quinoline-H, J = 4 Hz), 7.19-7.62 (m, 4H, Ar-H), 5.22 (s, 2H, O-CH₂), 3.59-3.62 (m, 2H, CH₂), 2.68-2.70 (m, 2H, CH₂) ppm; ^{13}C -NMR (100 MHz, DMSO- d_6) δ : 34.37, 40.6, 61.9, 112.4, 116.2, 117.2, 124.1, 125.1, 126.8, 130.4, 131.5, 132.2, 133.0, 140.8, 148.7, 150.9, 153.4, 161.5, 164.2, 169.5 ppm; Anal. Calcd for C₂₀H₁₇ClN₄OS: C, 60.53; H, 4.32; N, 14.12; Found: C, 60.61; H, 4.37; N, 14.08.

RESULTS AND DISCUSSION

The target compounds **4(a-d)** were synthesized by the base-catalyzed cyclization of carbothioamide derivatives **3(a-d)**. The quinolinyl carbothioamides were formed by the reaction between quinoline hydrazide and substituted aryl isothiocyanates **2(a-d)**. The starting material quinoline hydrazide was prepared by reacting 5-chloro-8-hydroxy quinolinol with ethyl chloroacetate resulted in the formation of aryloxy ester of quinolinol. This on further reaction with hydrazine hydrate gave corresponding acetohydrazide derivative (**1**). All the molecules were tested for their antioxidant and anticancer activity. The spectral analysis of starting material quinoline hydrazide derivative has shown characteristic stretching vibration at 1678 cm^{-1} and 3319 cm^{-1} corresponds to C=O and NH₂ group respectively. It was further confirmed by the ^1H and ^{13}C NMR characterization. Proton NMR studies show the signal at δ 4.39 and 4.76 ppm corresponds to N-H and -CH₂ protons. On reaction with isothiocyanates **2(a-d)**, the compound **1** forms corresponding carbothioamide derivatives **3(a-d)** which is evident from the NMR signal where there is an absence of NH₂ proton and signal corresponds to -OCH₂ is remained in the spectrum with the slight shift in the region of δ 4.7-4.9 ppm. Further, the compounds **3(a-d)** were cyclized to form the final product, quinoline triazole derivatives **4(a-d)**. The absence of the carbonyl group (C=O) in FTIR analysis confirmed the cyclization of carbothioamide derivatives.

Antioxidant Activity of Synthesized Compounds**DPPH Radical Scavenging Activity**

All the synthetic samples were dissolved in DMSO at 10 mM stock concentration and 50 μL was used for testing antioxidant activity at a final concentration of 250 μM . Out of eight samples, samples **3a**, **3b**, **3c**, and **4c** did not show significant antioxidant activity against DPPH free radical as shown in Table-1. The remaining samples, which showed high antioxidant activity was tested at different concentrations to find out the IC₅₀ values are represented in Table-2. Blanks were prepared for each sample by replacing DPPH with methanol and the dilutions of the samples were made in DMSO wherever required. All the experiments were repeated in triplicates.

Table-1: Antioxidant Activity of the Samples at 10 mM Concentration (Sample Volume 50 μL).

S. No.	Sample	Inhibition %
01	3a	44.25
02	3b	51.885
03	3c	40.89
04	3d	92.932
05	4a	77.347
06	4b	82.756
07	4c	58.101
08	4d	92.412

As shown in Table-1, compounds **3d** and **4d** have shown the best free radical scavenging behavior and are considered to be the potent antioxidants with the 92% inhibition. Which is also evident from the IC₅₀ values (Table-2).

The compound **3d** found to exhibit the most potent activity of all the synthesized molecules. The better activity of carbothioamide derivatives could be attributed to the open-chain structures with methylene

spacer group as well as the presence of a polar group that can interact better with the enzyme that is inhibited. On the other hand, the titled quinoline-triazole hybrid molecules **4(a-d)** have shown good to excellent antioxidant activity (on comparing with the standard) which can be accredited to the synergistic effect of two bioactive pharmacophore units in the same structure.

Table-2: Antioxidant Activity of the Samples represented in their IC₅₀ Values

S. No.	Synthetic Sample	Antioxidant activity (IC ₅₀ mM)
1	3d	0.096±0.005
2	4a	1.003±0.049
3	4b	0.881±0.030
4	4d	0.238±0.018
*	Std (Ascorbic Acid)	0.032±0.001

In- vitro Anticancer Activity (MTT Assay)

The stock solution was prepared by dissolving the synthesized compounds in DMSO as 10 mg/mL and was stored at -20 °C. The breast cancer cell line (MCF-7) was used for the *in vitro* anticancer study. Exponentially growing cells were collected from T- 25 tissue culture flasks and a stock cell suspension 1 X 10⁶ were prepared with respective media. Cells were seeded 5000 cells/well in sterile 96-well flat-bottom tissue culture plate and allowed to attach for 24 hours. After 24 hours of incubation, cells were treated with 100 µl of test compounds from the respective stock solution for 48 hours. To each well of the 96 well plates, 50 µl of MTT reagent (Stock: 2 mg/ml in PBS) was added and incubated for 3 hours at 37 °C. The optical density (O.D) was measured by a well plate reader at a wavelength of 540 nm. Percentage cell death of each compound was calculated by the formula below:

$$\% \text{ Cell Death} = \frac{OD \text{ of Control} - OD \text{ of Test}}{OD \text{ of Control}} \times 100$$

The results are tabulated as IC₅₀ in Table-3.

Table-3: Anticancer Activity of the Samples represented in their IC₅₀ Values.

S. No.	Compound	IC ₅₀ (µM)
1	3a	>200
2	3b	32.24±0.025
4	3c	160.7±0.02
5	3d	59.5±0.026
6	4a	63.26±0.003
8	4b	47.64 ±0.005
9	4c	187.8±0.032
10	4d	117.6±0.015
Standard	Doxorubicin	0.82 ±0.001

As evident from Table-3 compounds, **3b** has shown best cytotoxicity against MCF-7 cell lines at 32.24 µM concentration which is nearest to that of the standard doxorubicin (0.82 µM). Among triazoles, the compound **4b** having chlorophenyl ring as aromatic part in isothiocyanate has shown significant inhibition when compared to the other members of the series. The rest of all molecules of the series have exhibited poor inhibition activity against MCF-7 cell lines.

CONCLUSION

In conclusion, a new series of quinoline-[1, 2, 4]-triazole hybrid molecules were synthesized using various isothiocyanate derivatives and quinoline hydrazide. All molecules were tested for anticancer and antioxidant activities. Among them, **3d** and **4d** having phenethyl isothiocyanate substitution have shown significant antioxidant activity when compared to the standard ascorbic acid. Moderate growth inhibition is observed for MCF-7 cell lines. Interestingly, the observed results have shown that both the intermediate

carbothioamide derivative **3(a-d)** and the target compound **4(a-d)** found to have significant pharmacological responses because of which it can be considered for the further development of new antioxidant and anticancer lead molecules.

REFERENCES

1. I. A. Al-Masoudi, Y. A. Al-Soud, N. J. Al-Salihi and N. A. Al-Masoudi, *Chemistry of Heterocyclic Compound*, **42**, 1377(2006), DOI:10.1007/s10593-006-0255-3
2. P. P. Gadhave, N. S. Dighe, S. R. Pattan, P. Deotarse, D. S. Musmade and R. V. Shete, *Annals of Biological Research*, **1**, 82(2010).
3. C. H. Zhou and Y. Wang, *Current Medicinal Chemistry*, **19**, 239(2012), DOI: 10.2174/092986712803414213
4. J. K. Sahu, S. Ganguly and A. Kaushik, *Chinese Journal of Natural Medicine*, **11**, 456(2013), DOI: 10.1016/S1875-5364(13)60084-9
5. S. G. Küçüküzümlü and P. Çıkla-Süzgün *European Journal of Medicinal Chemistry*, **97**, 830(2015), DOI:10.1016/j.ejmech.2014.11.033
6. Z. A. Kaplancikli, G. Turan-Zitouni, A. Ozdemir and G. Revial, *European Journal of Medicinal Chemistry*, **43**, 155(2008), DOI:10.1016/j.ejmech.2007.03.019
7. K. Zamani, K. Faghihi, M. R. Sangi and J. Zolgharnein, *Turkish Journal of Chemistry*, **27**, 119(2003).
8. S. G. Umut, G. K. Nesrin, G. Ozgur, K. Yavuz, K. Ekrem, I. Samil, A. Goknur and O. Meral, *Bioorganic and Medicinal Chemistry*, **15**, 5738(2007), DOI:10.1016/j.bmc.2007.12.012
9. B. S. Holla, N. K. Poorjary, S. B. Rao and M. K. Shivananda, *European Journal of Medicinal Chemistry*, **37**, 511(2002), DOI:10.1016/s0223-5234(02)01358-2
10. S. Eswaran, A. V. Adhikari, I. H. Chowdhury, N. K. Pal and K. D. Thomas, *European Journal of Medicinal Chemistry*, **45**, 3374(2010), DOI:10.1016/j.ejmech.2010.04.022
11. S. Kumar, S. Bawa and H. Gupta, *Mini Reviews on Medicinal Chemistry*, **9**, 1648(2009), DOI:10.2174/138955709791012247
12. S. Eswaran, A. V. Adhikari and N. S. Shetty, *European Journal of Medicinal Chemistry*, **44**, 4637 (2009), DOI:10.1016/j.ejmech.2009.06.031
13. R. S. Upadhyaya, J. K. Vandavasi, R. A. Kardile, S. V. Lahore, S. S. Dixit, H. S. Deokar, P. D. Shinde, M. P. Sarmah and J. Chattopadhyaya, *European Journal of Medicinal Chemistry*, **45**, 1854(2010), DOI:10.1016/j.ejmech.2010.01.024
14. Z. Xiao, S. L. Morris-Natschke, and K. H. Lee, *Medicinal Research Reviews*, **36**, 32(2016), DOI:10.1002/med.21377
15. R. M. Shaker, *Arkivoc*, **IX**, 59(2006), DOI:10.3998/ark.5550190.0013.101
16. M. Asadi-Samani, N. K. Farkhad, M. R. Mahmoudian-Sani and H. Shirzad, 2109, Antioxidants as a Double-Edged Sword in the Treatment of Cancer, Antioxidants, Emad Shalaby, IntechOpen, London, DOI:10.5772/intechopen.85468
17. F. Hayat, A. Salahuddin, S. Umar and A. Azam, *European Journal of Medicinal Chemistry*, **45**, 4669 (2010), DOI:10.1016/j.ejmech.2010.07.028
18. H. Hegde, C. Ahn, D. Shwetha, S. L. Gaonkar and N. S. Shetty, *Journal of Korean Chemical Society*, **61**, 291(2017), DOI:10.5012/jkcs.2017.61.5.291

[RJC-5669/2020]