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FULL PAPER

Synthesis, characterization, and *in vitro* activity of new prepared compunds derivatives from 6-aminqunoline-7-hydroxylic acid

Ahmed Sa'adi Hassan

Medical Lab Technique, College of Health and Medical Techniques, Middle Technical University, Baghdad, Iraq

In medical chemistry, aminoqunoline-7-hydroxylic acid is considered as a very useful and attractive nucleus supporting compound. Since then, it has become a central moiety in a variety of bioactive compounds. We synthesised new antioxidants from 6-aminoqunoline-7-hydroxylic acids and determined their antioxidant activity. In cellular and intracellular physiological responses, the peptides are usually considered as the main regulators and widely expected to be used in disease treatment. Due to their therapeutic significance, the two vital molecules, aminoqunolines and peptide derivatives have been combined together into a single molecule by changing the various amino acids synthesized by different chemical reactions. Analysis and valdation of such compunds by Fourier transform infrared (FTIR), ^{13}C and (^{1}H) nuclear magnetic resonance (NMR) spectra was done. The specific optical rotation (SOR) has also been determined. The evaluation of *in vitro* antioxidant activities of such multifunctional compounds was carried out using the DPPH and Nitric oxide free radical scavenging methods. Activity was noted for derivatives from 6-aminoqunoline-7-hydroxylic acid, while other members showed a higher antioxidant activities than the ascorbic acid. All the five compounds synthesized were studied for their potent antioxdinat activity. A2 and A3 showed highest DPPH scavenging activity at 4 µM. Activity was increased for A3 upto 63.3% and 66.8% on increasing the alkyl chains and polar side chains respctively. A1 was found to exhibit high nitric oxide scavenging activity with 31.2% of activity. This study confirmed the synthesis of new compounds through infrared and NMR spectra. Moreover, they are highly effective in scavenging free radicals.

***Corresponding Author:**
Ahmed Sa'adi Hassan
Email:drahmedhassan1974@mtu.edu.iq
Tel.: 07901857343

KEYWORDS

Quinazolinone; amino acids; antioxidant agents; benzoxizanone; DPPH activity.

Introduction

Scientists continuously uncover novel and thrilling uses for heterocyclic compounds in the ever-expanding field of heterocyclic chemistry. For the production of substituted 1,2,4-triazole-3-thiones, numerous synthetic processes are available. One of the key elements in organic synthesis is the creation of easy-to-use and effective methods to obtain five-membered heterocycles. Many of these compounds are synthesized and they are found to aid in developing novel drugs [1].

Antioxidant substances are essential as a component in health protection. Antioxidants may lower your chance of developing chronic

illnesses like cancer and heart disease, according to scientific research [1]. Vitamin C, vitamin E, carotenes, phytates, and phytoestrogens are just a few of the antioxidants that come from plants [2]. However, because of the potential synergistic interactions between the antioxidant compounds in the food mixture, is expensive and ineffective to separate the active component separately from food due to the complexity of food composition [3]. For rapid quantification of antioxidant efficacy in disease prevention, the development of novel synthetic powerful antioxidant compounds is crucial.

In mitochondrial membrane, ROS is produced by the electron transport chain (ETC), which is a chain of protein complexes found in mitochondria [3]. ROS accumulation has harmful effects on homeostasis and said to actively participate in a vicious circle resulting in the aggregation and misfolding of an uncontrolled inflammatory proteins, lipid per oxidations, over-activation of innate immune system elements like microglias and atrocities [4]. In addition to OS, metallostasis is the other major factor in both the rebellion and progressions of cell damages and participates in destabilization of the formation of vital structures such as proteins, lipids, and DNA [5,6].

Recent studies suggest that oxidative damages are the major causes of cone deaths in retinal pigmentosa (RP), although inflammations and OS are well-known characteristics of neurodegenerative disorders [7,8]. This fact established for studying the protective roles of phytonutrient in causing retinal disorders like diabetic retinopathy and RP [9, 10]. In preclinical RP models, some nutrients such as N-acetylcysteine (NAC) [11], sulforaphane [12], naringenin, and quercetin were shown to hinder retinal degenerations [13]. Importantly, the antioxidant tests utilized in our study assessed the synthesized compounds ability against scavenging 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical species. The absorption maximum at 516 nm was presented by the stable radical (DPPH). In this study, we present the design, synthesis, characterization, and evaluation of the antioxidant activity of the new derivatives of 6-aminoqunoline-7-hydroxylic acid. We studied the antioxidant evaluation by DPPH and nitric oxide free radical scavenging methods.

Materials and methods

All the chemicals and the desired compounds used in our study were obtained from SD fine and chemicals/ Merck Company. The results were determined in an open capillary tube. Melting points were determined in a Sigma melting point apparatus. The measurement of the compounds' infrared spectra was carrird out on a PE FTIR, in a KBr disk with the expression of the absorption bands was in cm^{-1}. The ^{1}HNMR spectra were calculated on Bruker Avance dpx-200 spectrometer (in 200 MHz) and CDCl3 as a solvent with the Tetra-methyl-silane (TMS) as internal references. All the reagents used were of high grade. The acetone, ethanol, sodium hydroxide, N-benzoyl glycine, and anthranilic acid were purchased from E-MERCK L.t.d, Mumbai, and proline and methionine were purchased from SISCO Research Labs. L.t.d, Mumbai, while Eddys Hot Plate Machine was purchased from Sigma, Chennai.

Chemistry

Preparation of 2-(4-metoxyphenyl-4H-benzo [1,3]oxazino[-4-5-g] quinolin-4one: About 0.05M 6-aminoqunoline-7-hydroxylic acid was added to 60 mL of pyridine and stirred well. To this mixture 4-methylbenzoyl chloride (0.05 M) was added rop by drop and maintained at 2-50 °C for 1 hour. The comtents were stirred thoroughly for 2 hours at room temperature until a solid product was formed. The sodium bicarbonate solution formed was

filtered, and the separated pale yellow solid was then washed twice with water and re-crystallized from ethanols. Yield: 89%, M.P: 117-119 C.

Method in General prepration of 2(4-OXO-2-phenylquinazoline-3(4H)-yl) substitution acetic acid: Aminoacids (histidine, tyrosine, phenylalanine, tryptophan, and piotin) were prepared in 10 ml of glacial acetic acid. About 0.01 M of selected amino acid with dried pyridine (10 ml) has been added into 2-(4-metoxyphenyl-4H-benzo[1,3]oxazino[-4-5-g]quinolin-4one (0.01 M) and refluxed for 4 hours. The contents were then poured into crushed ice and later incubated for 12 hours. The solid obtained was filtered and washed twice with cold water and then recrystallized from ethanols for obtaining 2(4-OXO-2-phenylquinazolin-3(4H)-yl) acetic acid (A2-A5). The compounds are synthesized using the above-mentioned method via condensation of 2(4-metoxyphenyl-4H-benzo [1,3] oxazino[-4-5-g]quinoline-4 one by various amino acids (tyrosine, histidine, phenylalanine, tryptophan, and piotin). The synthesis procedure is displayed in Figure 1.

Evaluation of *in vitro* antioxidant activity: The newly prepared interactions were evaluated with the stable free radicals of DPPH. Stabilized free radicals species DPPH are usually used to evaluate radical scavenging capability of various antioxidants. The paramagnetic compound DPPH, having odd electron, exhibit strong absorption at 517 nm. The absorbance decreases as the DPPH turns purple into yellow because of free radical scavenging by anti-oxidant substances via hydrogen donation to produce stable DPPH-H molecules. Solutions of various drugs (100 µM) are added to 100 µM of freshly prepared DPPH in 95% ethanol. The tubes are placed at ambient temperatures for about 20 min and the absorbance was noted at 517 nm. DPPH scavenging activity along with IC_{50} was calculated for various drugs in the study [14]. DPPH with ethanol served as control and ascorbic acid was used as positive control in the study. DPPH scavenging activity was calculated using the formula % inhibition = $(OD_{control} - OD_{test} / OD_{control}) \times 100$.

Nitric oxide free radical scavenging activity: The Ebrahimzadeh *et al.* (2008) method was used to assess the plant preparations' capacity to scavenge nitric oxide radicals. Using the Greiss reaction, nitric oxide was produced from sodium nitroprusside and quantified. Butylated Hydroxytoluene (BHT) was used as a standard. Nitric oxide synthase production is inhibited by BHT, a naturally occurring direct nitric oxide scavenger. It lessens the quantity of nitrite produced when oxygen reacts with the nitric oxide produced by sodium nitroprusside. The absorbance was measured at 596 nm and the percentage antioxidant activity was calculated using the formula in equation % inhibition = $(OD_{control} - OD_{test} / OD_{control}) \times 100$. Varying concentrations of the compunds were used in the study.

Statistical analysis

All the results are average of triplcates and expresed with standard deviation. $P<0.05$ was considered as significant throughout the study.

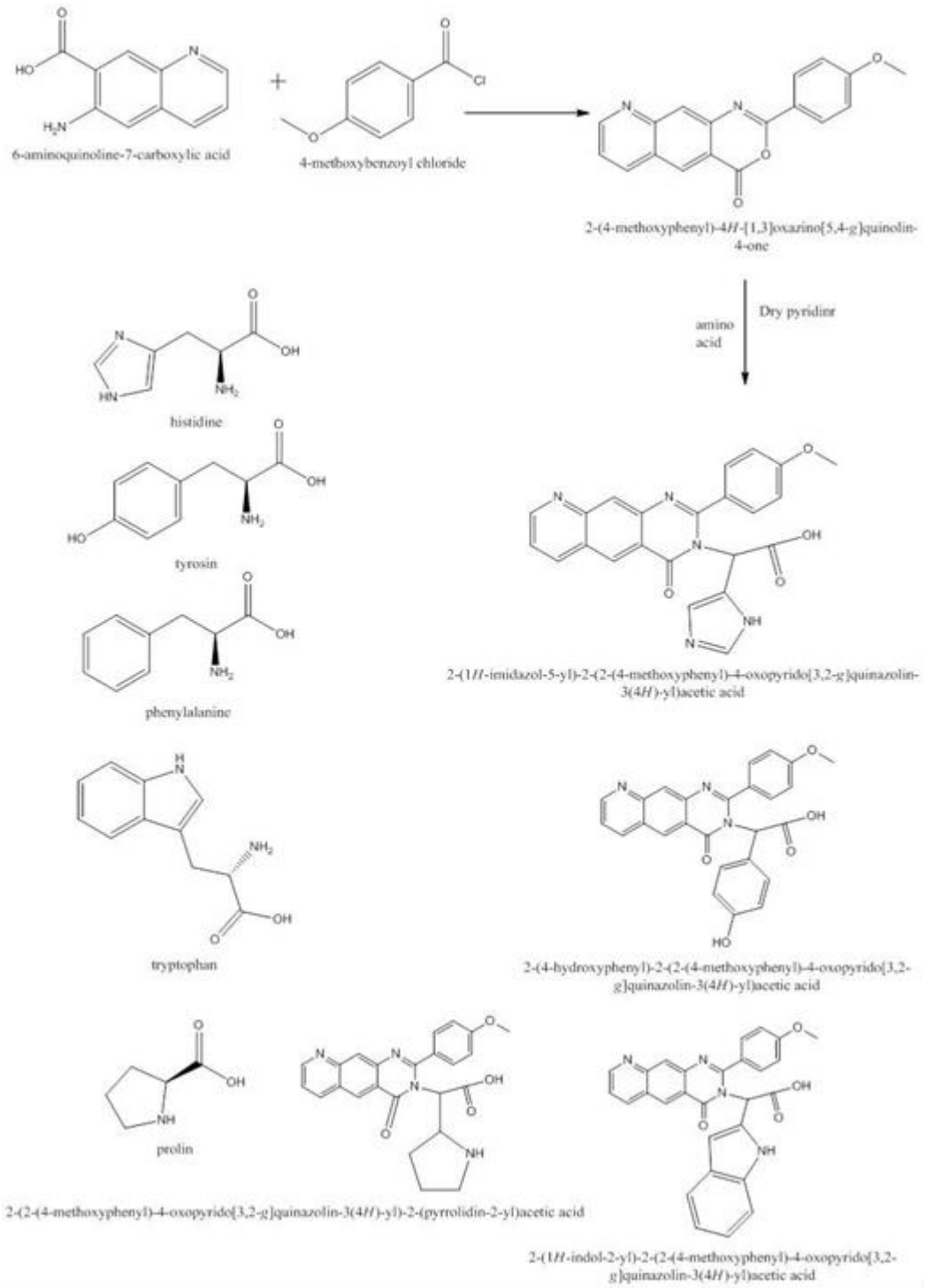

FIGURE 1 Diagrammatic representation of the synthesis procedure

Results and discussion

Chemistry: Five of the newly prepared compound (A1-A5) are synthesized with a yield ranging between (70-90%). However, A2 and A5 derivatives showed lowest yield (45%-50%). In our study, physical data including melting point and yield were also given. The derivatives of quinazolinone were characterized by analyzing the IR, ^{1}H-NMR and ^{13}C-NMR spectra. Infrared spectra (IR) displayed characteristic bands at spepcific wave numbers (KBr 3365) and for Ar–OH and O–Hstr at 2605-3255, respectively. O–Hstr,

COOH (3052-3056), Ar–Hstr (3052), C–Hstr, CH3 (2865, 2878), C = Ostr, COOH (1712), 1666 (C = Ostr, rings), 1569, 1565, 1413, 1417 (skeletal band), 1405 (O–Hdef, COOH), 865, 836, 765, 742, and 686 (C–Hdef, Ar), strong band at cm^{-1} due to C = O (in rings) stretchings, 3030-3085 cm^{-1} owing to C-H (Ar-H) stretching, 100-1567 cm^{-1} owing to C = C stretching (Ar).

For all the antioxidant compounds, ^{1}H-NMR spectra were taken for which supporting structures were assigned [23]. All the compounds exhibited multiples in the δ7.06-8.03 region because of the aromatic hydrogen (Ar-H). In addition, compound A1 exhibited a triple in the of δ 3.83 region due to –O-CH_3 protons and quartet in the δ 7.85-8.89 region owing to –CH- proton and a single in the region. Compound A2 displayed a triple in the region of δ 3.4 -3.8 due to (O- CH_3) protons. The spectra showed in Figures 2-5. Another singlet in the region of 8.37 and 13.2 due to (–NCH, NH) protons and singlet in the 11.07 region owing to –OH proton compounds. A3 exhibited a double in the δ 5.7,11.2 region due to O-H protons (CH-OH). The compound A4 displayed signals at δ=(12.6-) ppm belonging to (-CH-N-) proton [12] (Figures (3-6). The compound A5 displayed signals at δ=(2.2-) ppm belonging to (-CH-N-) proton [12] (Figures 3-8). ^{13}C-NMR compound spectrum of A1 displayed signal at δ=(55.8) ppm belonging to (CH_3) carbon signals at δ=55.2 ppm belonging to (-N-CH_2-CO-) carbon and signal at δ=(156-183) ppm belonging to (C=O) carbons [230b] (Figure 3-6). ^{13}C-NMR compound spectrum [A2] displayed signal at δ=(134.8,135.8) ppm belonging to (C-NH) carbon, signals at δ=162.2 ppm belonging to (-N-CH_2-CO-) carbon and signal at δ=(168) ppm belonging to (C=O) carbon [230b] (Figures 2-5).

^{13}C-NMR compound spectrum A3 displayed signals at δ=(55.8-52.8) ppm belonging to (CH_3) carbon, signals at δ=122.2-131.4 ppm belonging to (-CH_2-aromatic) carbon and signal at δ=(156-173) ppm belonging to (C=O) carbon[230b] (Figure (3-6). ^{13}C-NMR compound spectrum [A4] displayed signals at δ=(54.8-) ppm belonging to (CH_3) carbon, signals at δ=118.2-128.4 ppm belonging to (-CH_2-aromatic) carbon and signal at δ=(162-168) ppm belonging to (C=O) carbon [230b] (Figure (3-6). Finally ^{13}C-NMR compound spectrum [A5] displayed signals at δ=(53.2-) ppm belonging to (CH_3) carbon, signals at δ=122.2-146.4 ppm belonging to (-CH_2-aromatic) carbon, signal at δ=(161-174) ppm belonging to (C = O) carbon and signal at δ=(24-46) ppm belonging to (C-C) carbon of pyral rings[230b] (Figures 2-5).

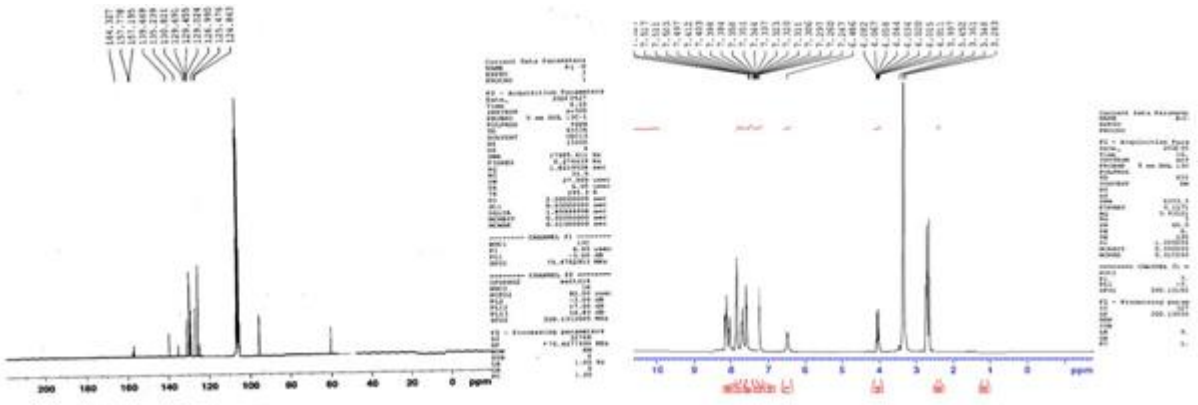

FIGURE 2 ^{1}H NMR and C^{13}-NMR spectra for compound A1

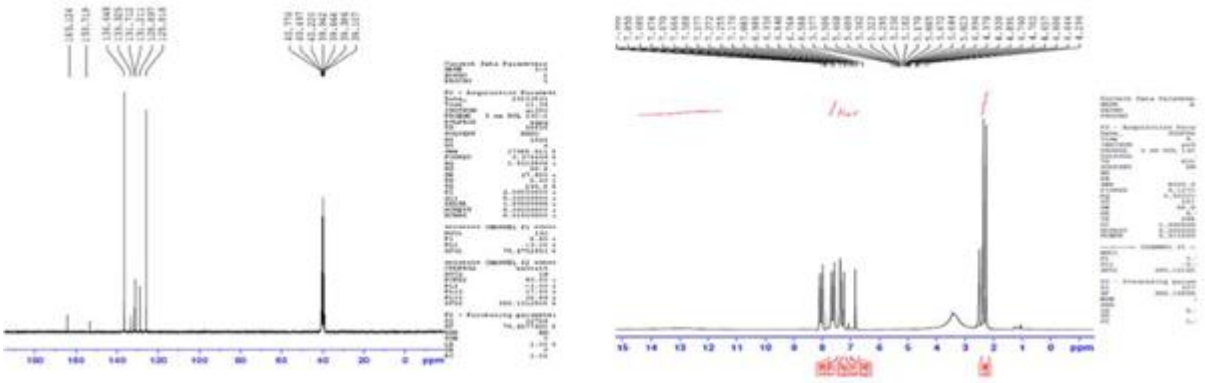

FIGURE 3 ^{1}H-NMR and ^{13}C-NMR spectra for compound A2

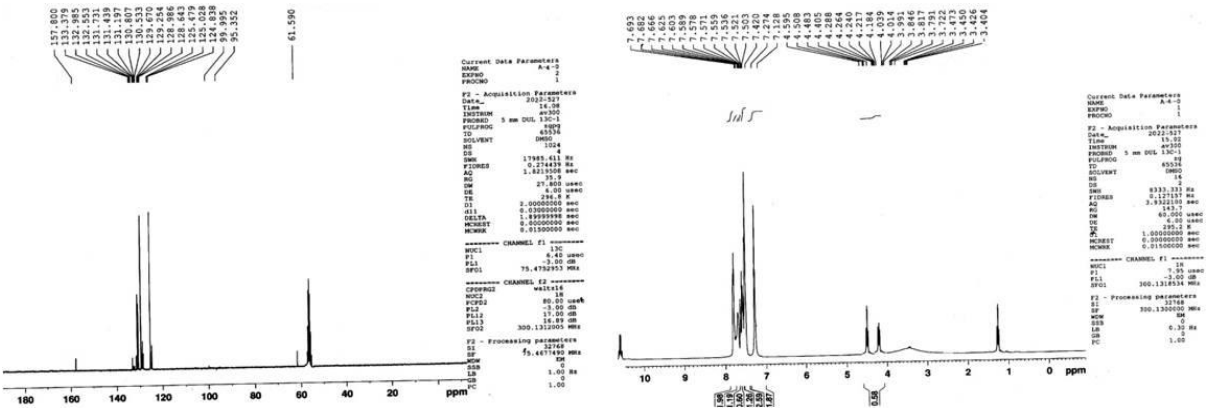

FIGURE 4 ^{1}H-NMR and C^{13}-NMR spectra for compound A3

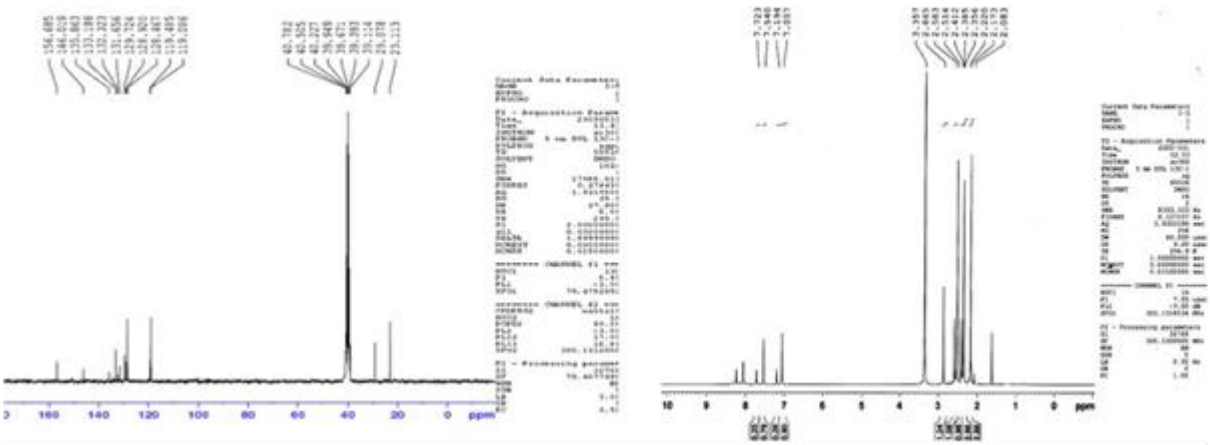

FIGURE 5 ^{1}H-NMR and ^{13}C-NMR spectra for compound A4

Evaluation of Antioxidant activity *in vitro* by DPPH: All of the compounds (A1-A5) have been screened for DPPH reductions. The highest activities were shown by A2 and A3 due to the moiety of guanidine group. Our findings showed that the compounds prepared at a concentration of 4 µM had highest reduction of 33% for both A2 and A3 the compound with simplest amio acid tyrosin, phenyalanine (A2 and A3) showed only activity. On increasing the alkyl chain, at a concentration of 8 µM, the activity was enhanced to 51.8 and 63.3%, resepctively, for A2 and A3. On introducing the polar side chain amino acid, at a concentration of 12 µM, A2 activity remained the same, while A5

exhibited 66.8% activity. On introducing tyrosine and proline and sulfhydryl which contained cysteines, an increase in activities was noticed especially for A4 which exhibited 62.4% activity. On introducing the polar side chain amino acid, at a concentration of 16 µM, A and A5 exhibited 68.2% and 65.8% activity, respectively.

The nitric oxide radical scavenging: All of the compounds (A1-A5) have been examined for nitric oxide free radical scavenging. Interestingly, the compounds showed the same activity pattern as in the case of DPPH reductions. The compound having the simplest amino acid glycine (A1) exhibited 31.2% of activity. On increasing the alkyl chain, the activity for A2, A3, and A5 was found to be 33.1,32.9, and 38.5%, respectively. On introducing the polar side chain amino acid e.g., the hydroxyl-containing serine, there was an increase in activities of tyrosine and proline and sulfhydryl containing cysteine where A4 showed 62.1% activity. The A2 showed the highest activity of 68.7%, with the moiety of guanidine group. All the results were demonstrated in Figure 6.

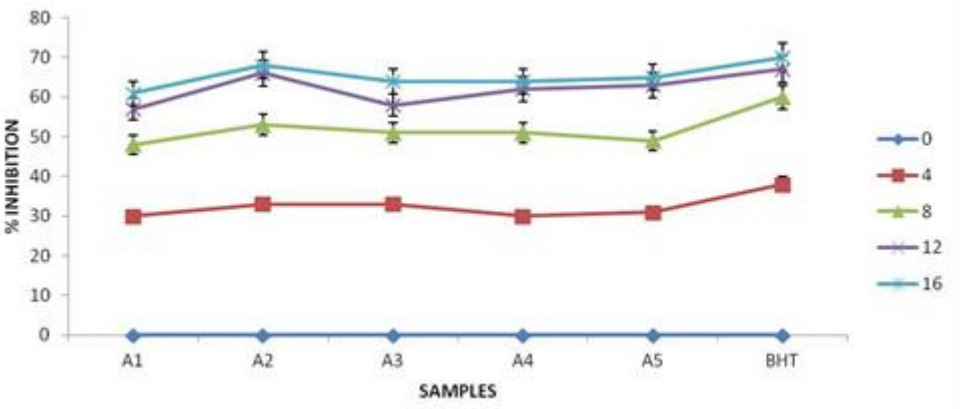

FIGURE 6 The nitric oxide scavenging assay of the compunds A1-A5 at varying concnetrations. All the values are average of three independent experiments

Due to the harmful function that free radicals play in biological systems, radical scavenging activities are extremely important [24]. Using a well-established assay like the DPPH free radical scavenging assay, the freshly synthesised compounds' *in vitro* antioxidant properties were evaluated at various concentrations [25]. Due to their capacity to donate hydrogen, antioxidants are thought to have an impact on DPPH radicals [25]. Antioxidant molecules have the ability to neutralise DPPH free radicals and turn them into products that are colourless or bleached, which reduces absorption. The *in vitro* antioxidant activity of the synthesised compounds A1 to A5 was studied with regard to standard Ascorbic acid and our findings confirmed that the newly synthesised compounds were potent antioxidant agents.

Similar studies were done by Jeleń, M. (2015), [26] where they synthesized new derivatives and found a very high antioxidant activity with IC_{50} in the range of 1 to 23 µM. 6-aminoquinoline-7-hydroxylic acid was used in synthesizing novel derivatives and very studied for their antioxdiant potential [27]. Kumar *et al.* (2010) reported very high nitrc oxide scavenging activity with 6-aminoquinoline- 7-hydroxylic acid as confirmed from NMR studies [28]. Kourounakis AP *et al.* (2008) also reported of the significant DPPH scavenging activity with the newly synthesized derivatives of 6-aminoquinoline-7-hydroxylic acid. Similar DPPH scavenging activity was also reported with the IC_{50} of 25µM [24,29]. Newly synthesized derivatives of the 6-

aminoquinoline-7-hydroxylic acid are proven very potent in antioxidant activity [30,31].

Conclusion

The results of this study showed that the synthetic method is easier and the compounds' yield rate (78-92%) was fairly good. All compounds showed moderate to significant antioxidant activity. The extreme significant activity was shown by compound A2. Existence of significant structural characteristics of good antioxidant in the synthesized compounds meets the criteria, and hence it proved to be a potent one. The continuous development of such strategies proves that drugs of quinazolinone peptide can be beneficial to treat different diseases associated with inflammation and free radicals.

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Conflict of interest

The authors declare that there is no conflict of interest in this article.

Ethical Clearance

This study was done under the supervision of the local Ethical Committee.

Orcid:

Ahmed Sa'adi Hassan:
https://orcid.org/0000-0002-1274-4176

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