ISSN 1070-3632, Russian Journal of General Chemistry, 2020, Vol. 90, No. 4, pp. 720–724. © Pleiades Publishing, Ltd., 2020.

Synthesis and Cytotoxicity of Quinazolin-4(3*H*)-one Based Peptides

P. Shankaraiah[a,b], A. K. D. Bhavani[a,*], A. Kishore Kumar[b], and K. Ramakrishna[a]

[a] *Department of Chemistry, University College of Science, Osmania University, Hyderabad, 500007 India*
[b] *Department of Humanities and Sciences, Vardhaman College of Engineering, Shamshabad, Hyderabad, Telangana, 501218 India*
**e-mail: shankarpou@gmail.com*

Received February 12, 2020; revised March 18, 2020; accepted March 21, 2020

Abstract—A novel series of quinazolin-4(3*H*)-one derivatives has been synthesized in high yields using the multicomponent Ugi reaction and characterized by IR, NMR and mass spectral data. The products have been tested for their cytotoxic activity against HeLa cells. Two tested compounds have shown potent activity compared to standard drug Doxorubicin. The in silico docking studies of the compounds against quinone reductase-2 (4ZVM) enzyme have also supported their activity.

Keywords: quinazolin-4(3*H*)-one, Ugi multicomponent reaction, cytotoxic, isocyanide

DOI: 10.1134/S1070363220040246

INTRODUCTION

Quinazolin-4(3*H*)-one is a building block of naturally occurring alkaloids and utilized as a drug like scaffolds in some natural products such as trypanthrin, rutaecarpine and luotonin A. Quinazolin-4(3*H*)-one and its derivatives demonstrate a wide range of biological activities including anti-tumor [1], anti-inflammatory [2], analgesic [3], and antimicrobial [4]. In the current study we have designed and synthesized quinazolin-4(3*H*)-one based peptides utilizing the Ugi multi-component reaction, and tested cytotoxicity of the products against cancer cell line (HeLa cells).

RESULTS AND DISCUSSION

6-Amino quinazolinone (**5**) was chosen as a precursor in development of a multifunctional aliphatic chain at the position-6 of quinazolin-4(3*H*)-one via the Ugi reaction [5]. The compound **5** was synthesized from isatin as presented in Scheme 1 [6–9]. A reaction of 6-amino quinazolin-4(3*H*)-one (**5**) with benzaldehyde (**6a**), benzoic acid (**7a**) and *tert*-butyl isocyanide (**8a**) in methanol gave the corresponding *N*-[2-(*tert*-butylamino)-2-oxo-1-phenylethyl]-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)benzamide (**9a**) in 76% yield. This multicomponent reaction was extended to different substituted aromatic aldehydes **6b**–**6e**, aromatic acids **7b**, **7c** and isocyanide **8b** that gave the corresponding quinazolin-4(3*H*)-one derivatives (**9b**–**9l**) (Scheme 1). The structure of products was confirmed by IR, NMR and mass spectral data. IR spectra of the products **9a**–**9l** demonstrated the characteristic bands for three different C=O groups in the range of 1740–1605 cm^{-1}. Formation of the amido groups was also confirmed by three characteristic signals in the range of 157.2–171.1 ppm of their ^{13}C NMR spectra. In ^{1}H NMR spectrum the benzylic proton signals were recorded between 6.15 and 6.65.

Cytotoxicity of the synthesized compounds. The in vitro cytotoxic activity of the newly synthesized quinazolin-4(3*H*)-one derivatives **9a**–**9l** was tested against human cervical carcinoma (HeLa) cells by using the MTT assay [10] and compared with the standard drug doxorubicin. The IC_{50} values of quinazolin-4(3*H*)-one-peptide derivatives **9a**–**9l** exhibited cytotoxic effect close to that of doxorubicin, which was particularly pronounced for compounds **9b** and **9g** (Table 1).

EXPERIMENTAL

Melting points were measured in open capillary tubes and are uncorrected. IR spectra (KBr discs) were recorded on a Perkin-Elmer 337 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini 400 or Bruker 100 spectrometers using $CDCl_3$ as a solvent and TMS as an internal standard. HRMS were measured on a Q-TOF mass spectrometer.

Synthesis of quinazolin-4(3*H*)-one-peptide derivatives 9a–9l. An isocyanide **8a**, **8b** (1.61 mmol) was added to a stirred mixture of 6-amino-3-methylquinazolin-4(3*H*)-one **5** (0.857 mmol) with appropriate substituted benzoic acid **7a**–**7c** (1.02 mmol) and aromatic aldehyde **6a**–**6e** (0.99 mmol) in methanol. The reaction mixture was heated at 60°C for 12 h. After completion of the process, as indicated by TLC, methanol was evaporated and the crude product was purified by column chromatography (eluent 20% ethyl acetate in petroleum ether) to afford the corresponding target product **9a**–**9l**.

***N*-[2-(*tert*-Butylamino)-2-oxo-1-phenylethyl]-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)benzamide (9a).** Yield 76%, white solid, mp 163–164°C. IR spectrum, ν, cm^{-1}: 3329 (N–H), 3065 (C–H, aromatic), 2923 (C–H, CH_2), 1734, 1672 br (C=O, amide), 1486 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.39 s (9H), 3.48 s (3H), 5.75 s (1H), 6.21 s (1H), 7.09–7.17 m (3H), 7.20–7.21 m (3H), 7.26–7.27 m (1H), 7.31–7.38 m (3H), 7.45–7.53 m (1H), 7.58–7.62 m (1H), 7.71 s (1H), 7.94 s (1H). ^{13}C NMR spectrum, δ, ppm: 28.6, 33.9, 51.7, 66.5, 121.3, 127.5, 127.8, 128.5, 128.6, 129.6, 130.0, 132.5, 133.1, 134.4, 135.6, 136.5, 140.1, 146.4, 147.0, 160.6, 168.4, 171.2. HRMS: 469.2116.

***N*-(*tert*-Butyl)-2-(2-chlorophenyl)-3-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)-4-oxo-4-phenylbutanamide (9b).** Yield 78%, white solid, mp 125–126°C. IR spectrum, ν, cm^{-1}: 3314 (N–H), 3062 (C–H, aromatic), 2975 (C–H, CH_2), 1728, 1673, 1640 (C=O, amide), 1533 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.41 s (9H), 3.47 s (3H), 5.72 s (1H), 6.56 s (1H), 7.01–7.16 m (5H), 7.29–7.33 m (5H), 7.66 d (J = 8.03, 1H), 7.83 s (1H), 7.89 d (J = 7.47 Hz, 1H). ^{13}C NMR spectrum, δ, ppm: 28.6, 33.9, 52.0, 62.8, 126.9, 127.3, 127.8, 127.9, 128.5, 128.9, 129.6, 129.7, 130.1, 137.5, 132.4, 135.4, 135.6, 136.4, 142.9, 146.6, 147.0, 160.6, 168.8, 171.1. HRMS: 503.18375.

***N*-[2-(*tert*-Butylamino)-1-(4-chlorophenyl)-2-oxoethyl]-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)benzamide (9c).** Yield 77%, white solid, mp 80–81°C. IR spectrum, ν, cm^{-1}: 3310 (N–H), 3063 (C–H, aromatic), 2985 (C–H, CH_2), 1728, 1673, 1640 (C=O, amide), 1433 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.39 s (9H), 3.49 s (3H), 5.85 s (1H), 6.17 s (1H), 7.09–7.23 m (7H), 7.28 d (J = 7.0 Hz, 2H), 7.36 d (J = 8.78 Hz, 1H), 7.56–7.60 m (1H), 7.77 s (1H), 7.94 d (J = 7.47 Hz ,1H). ^{13}C NMR spectrum, δ, ppm: 28.5, 33.8, 51.7, 60.9, 121.0, 127.3, 127.9, 128.1, 128.8, 129.1, 129.2, 130.6, 131.0, 131.8, 135.4, 137.9, 138.4, 146.9, 147.1, 160.5, 165.9, 171.7. HRMS: 503.18375.

Table 1. In vitro cytotoxicity (IC_{50}) of compounds **9a**–**9l** and doxorubicin

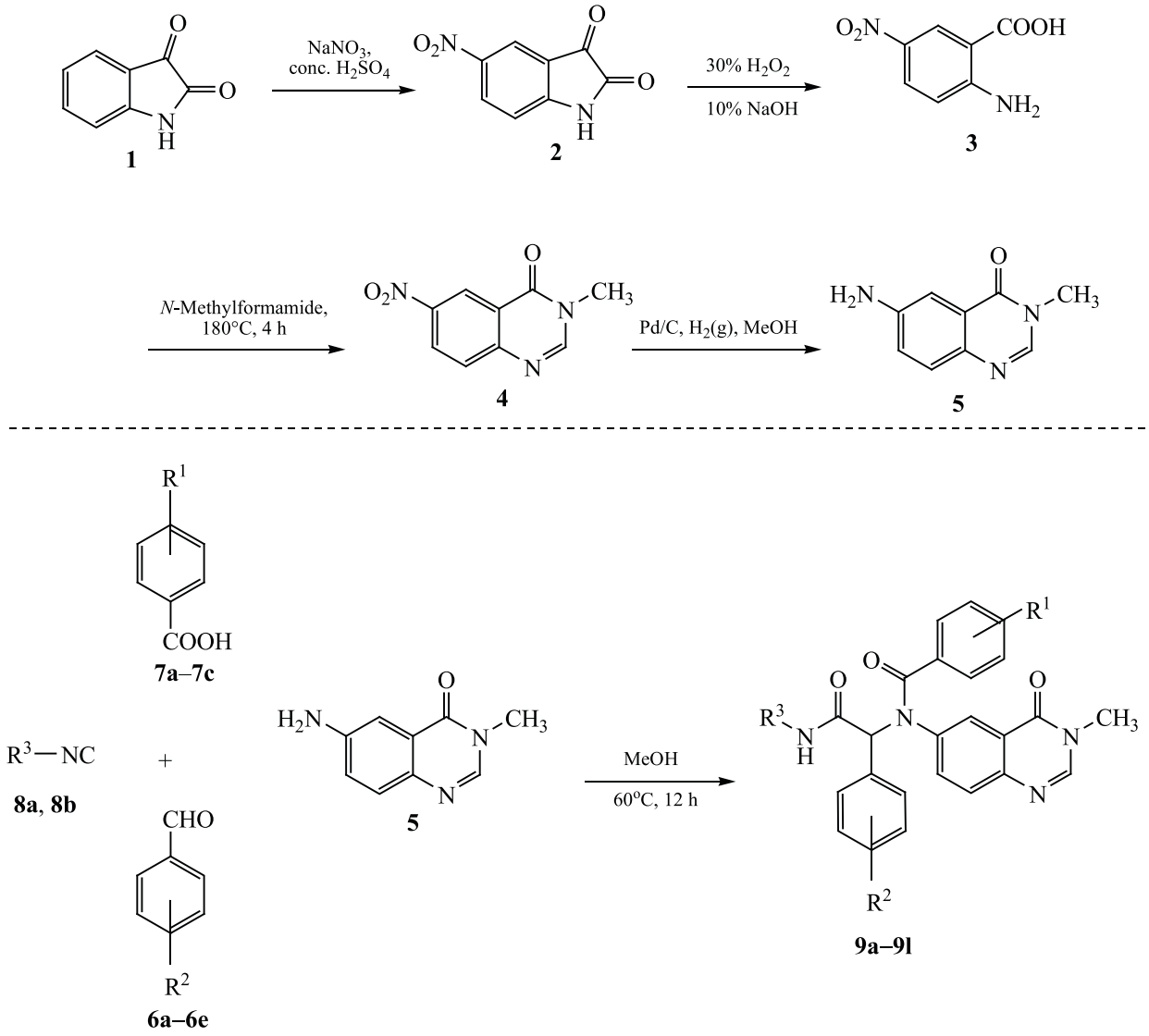
Compound	Concentration, μM				IC_{50} values, μM
	20	40	60	80	
9a	90	78	57	50	3.82
9b	78	65	45	42	3.00
9c	87	72	56	54	4.00
9d	97	80	73	56	4.51
9e	86	70	64	44	3.75
9f	98	80	68	44	3.72
9g	90	65	52	41	3.25
9h	86	71	54	44	3.46
9i	92	85	65	44	3.80
9j	86	70	64	44	3.75
9k	98	80	68	44	3.72
9l	82	67	55	44	3.43
Control[a]	100				
Doxorubicin	87	72	66	56	4.5

[a] HaLa cells not treated with the compounds.

***N*-[2-(*tert*-Butylamino)-1-(4-methoxyphenyl)-2-oxoethyl]-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)benzamide (9d).** Yield 83%, white solid, mp 130–131°C. IR spectrum, ν, cm^{-1}: 3331 (N–H), 3066 (C–H, aromatic), 2970 (C–H, CH_2), 1738, 1669, 1645 (C=O, amide), 1488 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.38 s (9H), 3.48 s (3H), 3.72 s (3H), 5.71 s (1H), 6.15 s (1H), 6.70–6.91 m (3H), 7.09–7.18 m (5H), 7.18–7.37 m (2H), 7.58 m (1H), 7.74 s (1H),7.92 d (J = 7.47 Hz, 1H). ^{13}C NMR spectrum, δ, ppm: 28.0, 33.4, 50.8, 54.5, 64.7, 113.2, 122.2, 123.6, 123.7, 126.7, 127.1, 127.8, 128.7, 130.8, 133.4, 133.9, 135.9, 146.7, 155.8, 160.8, 166.1, 168.4. HRMS: 499.23436.

***N*-[2-(*tert*-Butylamino)-2-oxo-1-phenylethyl]-4-chloro-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)-benzamide (9e).** Yield 73%, white solid, mp 110–111°C. IR spectrum, ν, cm^{-1}: 3329 (N–H), 3065 (C–H, aromatic), 2963 (C–H, CH_2), 1734, 1672 br (C=O, amide), 1486 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.38 s (9H), 3.49 s (3H), 5.68 s (1H), 6.19 s (1H), 7.08–7.10 m (2H), 7.19–7.27 m (7H), 7.38 d (J = 8.69 Hz, 1H), 7.60–7.69 m (2H), 7.94 d (J = 7.47 Hz, 1H). ^{13}C NMR spectrum, δ, ppm: 28.6, 33.9, 51.8, 66.5, 121.5, 124.7, 127.6, 128.1, 128.6, 130.0,

Scheme 1. Synthetic approach to quinazolin-4(3*H*)-one based peptides **9a**–**9l**.



R^1 = H, R^2 = H, R^3= *t*-Bu (**9a**), R^1 = H, R^2 = 2-Cl, R^3= *t*-Bu (**9b**); R^1 = H, R^2 = 4-Cl, R7 = *t*-Bu (**9c**), R^1 = H, R^2 = 4-OCH_3, R^3 = *t*-Bu (**9d**); R^1= 4-Cl, R^2 = H, R^3 = *t*-Bu (**9e**), R^1 = H, R^2 = H, R^3 = cyclohexyl **(9f)**; R^1 = H, R^2 = 4-Br, R^3 = cyclohexyl (**9g**), R^1 = H, R^2 = 2-Cl, R^3 = cyclohexyl (**9h**); R^1 = H, R^2 = 4-Cl, R^3= cyclohexyl (**9i**), R^1 = H, R^2 = 4-OCH_3, R^3 =cyclohexyl (**9j**); R^1 = H, R^2 = 3,4,5,Tri-OCH_3, R^3 = cyclohexyl (**9k**), R^1 = 2-NO2, R^2 = H, R^3 = cyclohexyl (**9l**).

130.1, 134.1, 134.2, 134.3, 135.6, 136.3, 139.8, 146.7, 147.1, 160.6, 168.3, 170.1. HRMS: 503.2101.

***N*-[2-(Cyclohexylamino)-2-oxo-1-phenylethyl]-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)-benzamide (9f).** Yield 73%, white solid, mp 123–124°C. IR spectrum, ν, cm^{-1}: 3268 (N–H), 3025 (C–H, aromatic), 2925 (C–H, CH_2), 1736, 1679, 1651, (C=O, amide), 1495 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.13–1.42 m (7H), 1.86–2.01 m (3H), 3.48 s (3H), 3.84–3.94 m (1H), 5.72 d (*J* = 7.85 Hz, 1H), 6.27 s (1H), 7.08–7.15 m (3H), 7.21–7.25 m (3H), 7.27–7.37 m (5H), 7.58–7.60 m (1H), 7.69 s (1H), 7.91 d (*J* = 7.47 Hz, 1H). ^{13}C NMR spectrum, δ, ppm: 24.1, 25.1, 32.2, 33.4, 48.0, 64.0, 120.4, 126.3, 127.7, 127.8, 127.9, 129.1, 130.0, 131.7, 133.3, 135.1, 136.4, 136.8, 138.8, 146.1, 148.5, 159.9, 168.4, 169.8. HRMS: 495.3814.

***N*-[1-(4-Bromophenyl)-2-(cyclohexylamino)-2-oxoethyl]-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)benzamide (9g).** Yield 74%, white solid, mp 167–168°C. IR spectrum, ν, cm^{-1}: 3270 (N–H), 3027

(C–H, aromatic), 2925 (C–H, CH_2), 1739, 1678, 1647 (C=O, amide), 1486 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.05–1.44 m (7H), 1.90–2.01 m (3H), 3.50 s (1H), 3.86–3.90 m (1H), 5.82 d (*J* = 7.78 Hz, 1H), 6.19 s (1H), 7.09–7.19 m (5H), 7.29–7.45 m (5H), 7.55–7.57 m (1H), 7.76 m (1H), 7.77 s (1H), 7.93 d (*J* = 8.37 Hz, 1H). ^{13}C NMR spectrum, δ, ppm: 24.6, 25.3, 32.7, 34.0, 48.9, 65.4, 121.6, 122.8, 127.5, 127.8, 128.4, 129.7, 131.6, 131.7, 133.3, 135.2, 136.1, 139.9, 146.6, 147.2, 160.5, 167.9, 171.3. HRMS: 573.14996.

***N*-[1-(2-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl]-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)benzamide (9h).** Yield 74%, white solid, mp 158-159°C. IR spectrum, ν, cm^{-1}: 3303 (N–H), 3067 (C–H, aromatic), 2930 (C–H, CH_2), 1740, 1657 br (C=O, amide), 1484 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.08–1.45 m (7H), 1.92–2.10 m (3H), 3.46 s (3H), 3.89–3.98 m (1H), 5.75 d (*J* = 7.69 Hz, 1H), 6.65 s (1H), 6.93–7.15 m (5H), 7.27–7.34 m (4H), 7.40–7.55 m (1H), 7.65–7.67 m (1H), 7.79 s (1H), 7.88 d (*J* = 8.17 Hz, 1H). HRMS: 529.19916.

***N*-[1-(4-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl]-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)benzamide (9i).** Yield 74%, white solid, mp 184–185°C. IR spectrum, ν, cm^{-1}: 3303 (N–H), 3089 (C–H, aromatic), 2927 (C–H, CH_2), 1738, 1661 br (C=O, amide), 1488 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.07–1.43 m (7H), 1.88–2.08 m (3H), 3.48 s (3H), 3.86–3.95 m (1H), 5.81 d (*J* = 7.58 Hz, 1H), 6.58 s (1H), 6.99–7.02 m (1H), 7.09–7.16 m (3H), 7.29–7.35 m (5H), 7.40–7.52 m (1H), 7.59–7.65 m (1H), 7.91 d (*J* = 7.57 Hz, 1H), 7.87 s (1H). ^{13}C NMR spectrum, δ, ppm: 24.5, 28.9, 32.0, 33.3, 49.6, 57.8, 105.5, 122.3, 123.3, 128.1, 129.2, 130.2, 131.0, 134.9, 140.8, 143.4, 143.8, 143.9, 151.6, 157.2, 160.6, 171.4. HRMS: 529.19916.

***N*-[2-(Cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl]-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)benzamide (9j).** Yield 82%, white solid, mp 172–173°C. IR spectrum, ν, cm^{-1}: 3394 (N–H), 3063 (C–H, aromatic), 2933 (C–H, CH_2), 1710, 1688, 1656 (C=O, amide), 1507 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.06–1.40 m (7H), 1.90–2.00 m (3H), 3.48 s (3H), 3.73 s (3H), 3.87–3.89 m (1H), 5.70 d (*J* = 7.47 Hz, 1H), 6.22 s (1H), 6.72–6.73 d.d (*J* = 1.58 Hz, 8.54 Hz, 2H), 7.08–7.37 m (8H), 7.58–7.60 m (1H), 7.73 s (1H), 7.91 d (*J* = 7.47 Hz, 1H). HRMS: 525.2812.

***N*-[2-(Cyclohexylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl]-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)benzamide (9k).** Yield 85%, white solid, mp 239-240°C. IR spectrum, ν, cm^{-1}: 3201(N–H), 3065 (C–H, aromatic), 2932 (C–H, CH_2), 1738, 1665 br (C=O, amide), 1488 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.08–1.42 m (7H), 1.89–2.04 m (3H), 3.48 s (3H), 3.69 s (6H), 3.76 s (3H), 3.86–3.94 m (1H), 5.79 d (*J* = 8.06 Hz,1H), 6.21 s (1H), 7.08–7.17 m (4H), 7.31–7.38 m (3H), 7.47–7.54 m (1H), 7.61 d (*J* = 7.70 Hz, 1H), 7.75 s (1H), 7.92 d (*J* = 7.47 Hz, 1H). ^{13}C NMR spectrum, δ, ppm: 24.8, 25.4, 32.7, 33.9, 49.0, 65.4, 121.5, 124.2, 127.1, 127.7, 128.0, 128.5, 128.6, 128.7, 129.5, 130.3, 132.6, 133.7, 135.8, 138.1, 145.2, 147.2, 147.4, 160.3, 167.5, 167.9. HRMS: 585.2805.

***N*-(2-(Cyclohexylamino)-2-oxo-1-phenylethyl)-*N*-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)-2-nitrobenzamide (9l).** Yield 72%, light yellow solid, mp 143–144°C. IR spectrum, ν, cm^{-1}: 3299 (N–H), 3098 (C–H, aromatic), 2931 (C–H, CH_2), 1738, 1664 br (C=O, amide), 1490 (Ar-H). ^{1}H NMR spectrum, δ, ppm: 1.11–1.43 m (7H), 1.94–2.05 m (3H), 3.46 s (3H), 3.89–3.96 m (1H), 5.83 d (*J* = 7.62 Hz, 1H), 6.36 s (1H), 7.20–7.23 m (4H), 7.26–7.32 m (4H), 7.41–7.46 m (3H), 7.88 s (1H), 7.90 d (*J* = 8.24, 1H). ^{13}C NMR spectrum, δ, ppm: 24.7, 24.8, 25.4, 33.2, 33.96, 49.0, 65.4, 121.5, 124.2, 127.1, 127.7, 128.0, 128.5, 128.6, 128.7, 129.5, 130.3, 132.6, 133.7, 135.8, 138.1, 145.2, 147.4, 160.3, 167.5, 167.9. HRMS: 540.2367.

Biological activity. The synthesized quinazolin-4(3*H*)-one derivatives **9a**–**9l** cytotoxicity was tested in vitro using the method of viability staining by trypan blue dye exclusion on HeLa cancer cells. The cells were seeded in 96-well plates. Each concentration of the compounds was seeded, and triplicate plates were used. Then, the cells were incubated at 37°C in the atmosphere of CO_2. After 24 h, the medium was replaced by fresh medium containing different concentrations of the synthesized compounds. The percent viability and cytotoxicity were calculated.

Cytotoxicity of the samples was measured by microculture tetrazolium (MTT) assay [10]. Stock solutions of compounds **9a**–**9l** were applied to make a series of dilutions (20, 40, 60, and 80 μM) with a final DMSO concentration of 0.1% and tested in quadruplicate in a CO_2 incubator. After 48 h of incubation, cell viability was determined by adding tetrazolium salt (Sigma) as a cytotoxicity indicator. After 24 h of incubation, 10 mm^3 of MTT (5 mg/cm^3) in phosphate buffered saline (PBS) were added to each well and incubated at 37°C for 4 h. The medium with MTT was then flicked off, and the

formed formazan crystals were solubilized in 100 mm^3 of DMSO. The absorbance at 570 nm was measured using a micro-plate reader.

CONCLUSIONS

Novel quinazolin-4(3*H*)-one based dipeptide derivatives have been synthesized, and their structures have been characterized by IR, NMR and mass spectral data. Concentration dependent cytotoxicity studies in HeLa cells have revealed toxicity of all compounds particularly **9b** and **9g**.

ACKNOWLEDGMENTS

P. Shankaraiah thanks to UGC, New Delhi, India for providing research fellowship and Department of chemistry, Osmania University for providing research facilities.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Chinigo, G.M., Paige, M., Grindrod, S., Hamel, E., Dakshanamurthy, S., Chruszcz, M., Minor, W., and Brown, M.L., *J. Med. Com.,* 2008, vol. 51, p. 4620. https://doi.org/10.1021/jm800271c
2. Amin, K., Kamel, M., Anwar, M., Khedr, M., and Syam, Y., *Eur. J. Med. Chem.,* 2010, vol. 45, p. 2117. https://doi.org/10.1016/j.ejmech.2009.12.078
3. Abbas, S.E., Awadallah, F.M., Ibrahin, N.A., Said, E.G., and Kamel, G.M., *Eur. J. Med. Chem*., 2012, vol. 53, p. 141. https://doi.org/10.1016/j.ejmech.2012.03.050
4. Al-Omary, F.A., Abou-Zeid, L.A., Nagi, M.N., Habib, E.-S.E., Alaa, A.-M., El-Azab, A.S., Abdel-Hamide, S.G., Al-Omar, M.A., Al-Obaid, A.M., and El-Subbagh, H.I., *Bioorg. Med. Chem.,* 2010, vol. 18, p. 2849. https://doi.org/10.1016/j.bmc.2010.03.019
5. Domling, A., Wang, W., and Wang, K., *Chem. Rev*., 2012, vol. 112, p. 3083. https://doi.org/10.1021/cr100233r
6. Kilic-Kurt, Z., Bakar, F., and Olgen, S., *Arch. Pharm.,* 2015, vol. 348, p. 715. https://doi.org/10.1002/ardp.201500109
7. Montoya-Pelaez, P.J., Uh, Y.-S., Lata, C., Thompson, M.P., Lemieux, R.P., and Crudden, C.M., *J. Org. Chem.,* 2006, vol. 71, p. 5921. https://doi.org/10.1021/jo060553d
8. Kulkarni, S.S., Singh, S., Shah, J.R., Low, W.-K., and Talele, T.T., *Eur. J. Med. Chem.* 2012, vol. 50, p. 264. https://doi.org/10.1016/j.ejmech.2012.02.001
9. Polishchuk, P.G., Samoylenko, G.V., Khristova, T.M., Krysko, O.L., Kabanova, T.A., Kabanov, V.M., Kornylov, A.Y., Klimchuk, O., Langer, T., and Andronati, S.A., *J. Med. Chem.,* 2015, vol. 58, p. 7681. https://doi.org/10.1021/acs.jmedchem.5b00865
10. Łukowska-Chojnacka, E., Patrycja, W., Monika, W., and Maria, B., *Monatsh Chem*., 2016, vol. 147, p. 1789. https://doi.org/10.1007/s00706-016-1785-8