RESEARCH ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

Synthesis and Assessment of Biological Activity of Quinazolinone-4(3*H*)-one Derivatives as Potential Anticancer Agents

Baljeet Singh[1*], Shailesh Sharma[2], Manish Sinha[3], S. Sagar[4]

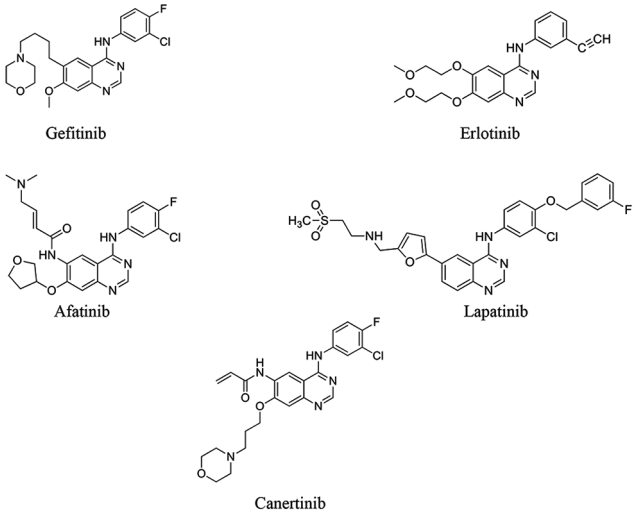
Abstract

One of the foremost causes of death around world is cancer. Hence, there is a continuous research going on to find newer anticancer agents with least side effect. Quinazolinone is a privileged framework with prominent anticancer activities. A sequence of eight derivatives (5a-5h) of quinazolinone-4(*3H*)-one was prepared and tested for activity as anticancer agents against MCF-7 cell lines in this study. One of the compounds 5e showed good activity with 63.71% inhibition of cell growth as compared to 86.96% inhibition by standard doxorubicin.

Keywords: Anticancer agents, Breast cancer, cell lines, MCF-7, Quinazolinone-4(3H)-one

Introduction

Cancer is an extremely proliferative disease that can spread to many organs. Cancer is the second main cause of death in the world, following cardiovascular disease, accounting for about 13% of all deaths per year.[1] "Globally, among every six persons, one is victim of cancer. Most fatal types of cancers include colorectal cancer, stomach cancer, liver cancer, breast cancer, and lung cancer. Global cancer occurrence is predicted to reach 22 million cases per year by 2030."[2] New chemotherapeutic medicines that may prevent cell growth are being investigated continuously because existing chemotherapeutic medicines are not fully capable to halt the progression of this horrible illness.[3] Quinazolinone is a privileged framework with a broad range of biological functions, including anticancer,[4-7] antimicrobial,[8-11] anti-inflammatory,[12-15] antiviral,[16-18] analgesic,[14,19-21] antidiabetic,[22-24] anti-tussive effects,[25] and anticonvulsant activities.[20,26-29] Quinazolinone derivatives are one of the promising agents for anticancer activity. Canertinib, erlotinib, lapatinib, gefitinib, and afatinib are some of the anticancer drugs which are based on quinazolinone nucleus and act through EGFR inhibition to treat cancer.[3,30]



Similarly, Mahdy *et al.* have reported a set of derivatives of quinazolin-4(3*H*)-one derivatives and evaluated them for antiproliferative effect against various cell lines including HepG-2, MCF-7, and HCT-116. Compound **I** was discovered to be effective against all cell lines with IC_{50} value of 3.97 ± 0.2, 4.58 ± 0.3, and 4.83 ± 0.2, respectively, in comparison to a standard drug doxorubicin with IC_{50} value of 4.50 ± 0.2, 4.17 ± 0.2, and 5.23 ± 0.2, respectively. It was further tested for tested for VEGFR-2 inhibition and was found almost equally active with IC_{50} value of 2.5 ± 0.04 μM as compared to sorafenib (IC_{50}=2.4 ± 0.05 μM)[1]. Le *et al.* have reported compounds **II** (IC_{50} = 17.08 ± 3.61) and **III** (IC_{50} = 13.29 ± 1.12) with better *in vitro* anti-tumor activity than standard drug gefitinib (IC_{50} = 30.40 ± 0.34) against PC3 (prostate cancer) human cell lines. "Sabry *et al.* synthesized 6-substituted amido, azo, or thioureido-quinazolin-4*(3H)*-one derivatives and evaluated for their *in vitro* anticancer activity. Compounds **IV**, **V,** and **VI** showed broad-spectrum antitumor activity with average IC_{50} values of 6.7, 7.6, and 9.1 μM, respectively, against methotrexate with IC_{50} value of 19.26 μM."[31] Rakesh *et al.* reported *in vitro* anticancer activity of compounds **VI, VII, VIII, IX, X,** and **XI** 32, 33, 34, 41, 42, and 43 (IC_{50} = 32.01 ± 1.17, 29.12 ± 1.33, 31.11 ± 1.19, 26.22 ± 0.69, 28.22 ±

[1]Research Scholar, IKG Punjab Technical University, Kapurthala, Punjab, India

[2]Department of Pharmaceutical Sciences, ASBASJSM College of Pharmacy, Bela, Punjab, India

[3]Scientific Officer, Government Drug Testing Laboratory, Department of AYUSH, Gwalior, Madhya Pradesh, India

[4]Scientist, Skanda Life Sciences Pvt Ltd, R and D Center, Bengaluru, Karnataka, India

Corresponding Author: Baljeet Singh, C/O Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, VPO Bela, Ropar - 140 111, Punjab, India. Tel.: +91-9464522048. E-mail: singhbaljeet8688@gmail.com

How to cite this article: Singh B, Sharma S, Sinha M, Sagar S. Synthesis and Assessment of Biological Activity of Quinazolinone-4(3*H*)-one Derivatives as Potential Anticancer Agents. Asian Pac. J. Health Sci., 2021;8(4):214-220.

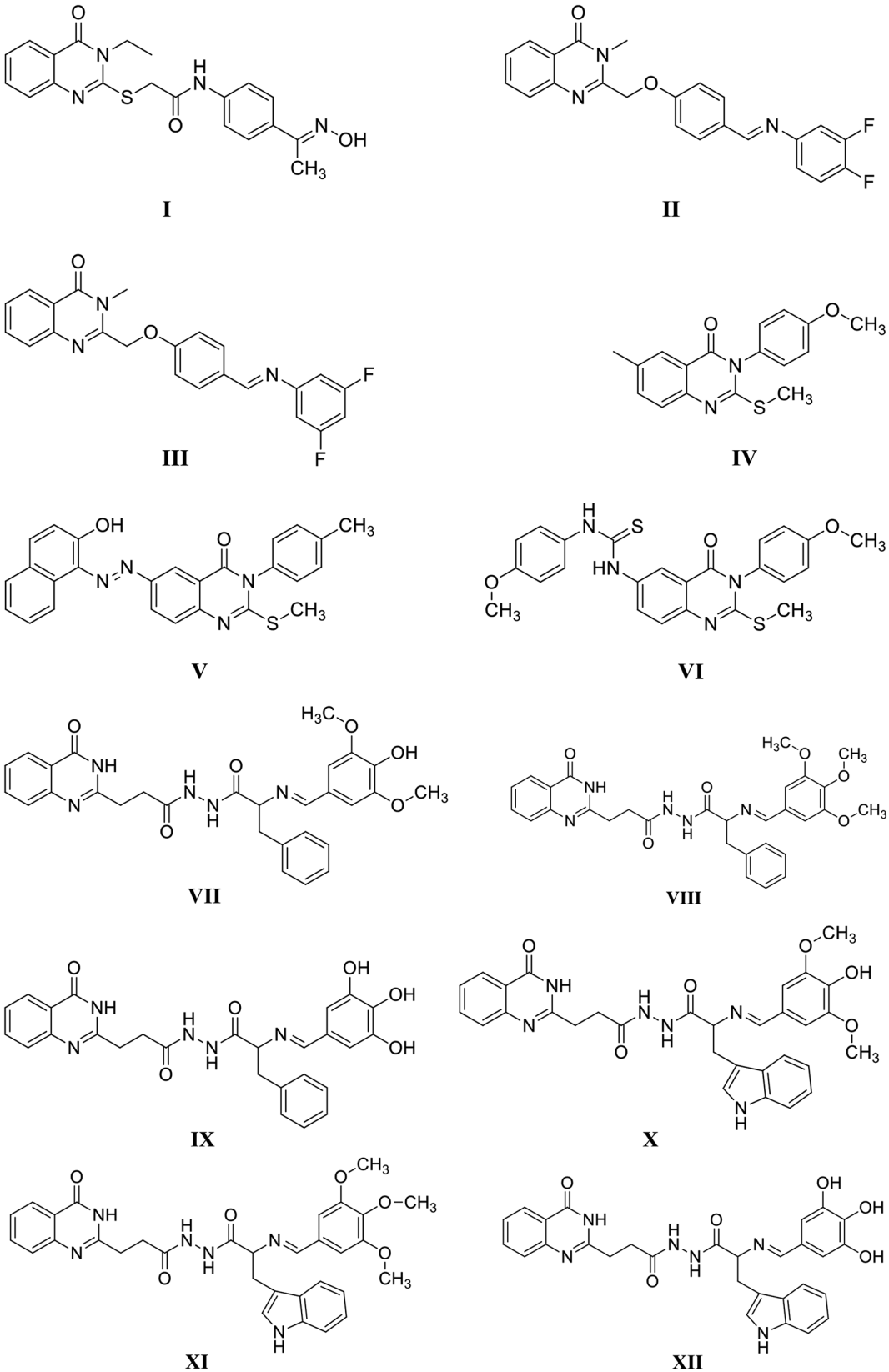
Source of support: Nil

Conflicts of interest: None.

Received: 20/07/21 **Revised:** 19/08/21 **Accepted:** 21/09/21

1.30, and 30.34 ± 1.08 µg/mL, respectively),which showed potent antitumor affect against MCF7 cell lines, compared to doxorubicin (IC_{50}=32.67 ± 1.09).[4]

Despite promising advances in clinical cancer therapy, current medications have adverse effects, including multidrug resistance, weak sensitivity, and extensive side effects, and have unable to



I **II** **III** **IV** **V** **VI** **VII** **VIII** **IX** **X** **XI** **XII**

eradicate tumors or inhibit their comeback.[32] Thus, in our current work, we prepared new variants of quinazolin-4(3*H*)-one and screened them on MCF7 cell lines to come out with new molecules san side effect of previous drugs.

Materials and Methods

Materials

Chemicals of LR grade were used for synthesis, which were procured from Spectrochem Pvt. Ltd. and Loba Chemicals Pvt. Ltd. Anthranilamide was procured from Sigma-Aldrich. Solvents of LR grade were used and were purified before use. Reactions were performed in dry glassware in an open air environment. Course of reaction was studied using thin-layer chromatography (TLC) with silica gel pre-coated plates (0.25 mm) with F254 indicator. The chromatogram was generated using a solvent solution with chloroform: methanol in varying ratios. Bruker 400 was used to capture ^{1}H-NMR spectra (400 MHz) and ^{13}C-NMR (100 MHz) at IIT Ropar, Punjab. Internal standards for ^{1}H-NMR were tetramethylsilane (0.0 ppm). The following pattern was used to report proton spectra: (proton position, multiplicity, J (coupling constant), and proton count). Multiple peaks are denoted with letters "s" for singlet, "d" for doublet, "t" for triplet, and "m" for multiplet. The infrared (IR) spectrum was captured using a Bruker Fourier transform IR-attenuated total reflection Alpha-E at ASBASJSM College of Pharmacy, Bela. All melting points were calculated using open end glass capillaries and are reported uncorrected.

Synthesis of Quinazolinone-4(3H)-one Derivatives

The reaction scheme shown in Figure 1 was used for the preparation of quinazolinone-4(3*H*)-one derivatives. The substituents are described in Table 1.

Where R= H, OCH_3 and R_1 = H, Cl, CH_3, NO_2

Reagents and reaction conditions: (i) DMSO, stirring at 100 °C, (ii) 4N HCl, reflux for 3 h, (iii) DMF, K_2CO_3

Procedure for Preparation of 2-phenylquinazolin-4(3H)-one Derivatives 2(a-b)

"Derivatives of 2-phenylquinazolin-4(3*H*)-one 2(a-d) were synthesized in accordance with the scheme devised by Na Yeun Kim and Cheol-Hong Cheon.[33] In 20 ml of DMSO, 0.05 mol (1.0 equivalent) anthranilamide and 0.06 mol (1.2 equivalent) substituted aldehyde 1(a-b) were dissolved in a flat bottom flask. After that, the solution was agitated for 12–18 h at 100°C. Reaction completion was tracked with the help of TLC technique and after completion, stirring was stopped and reaction mixture was cooled until it attained room temperature. To resulting solution,

Table 1: Substituents of compounds 5 (a-h)

Compound	R	R_1
5a	H	H
5b	H	Cl
5c	H	CH_3
5d	H	NO_2
5e	OCH_3	H
5f	OCH_3	Cl
5g	OCH_3	CH_3
5h	OCH_3	NO_2

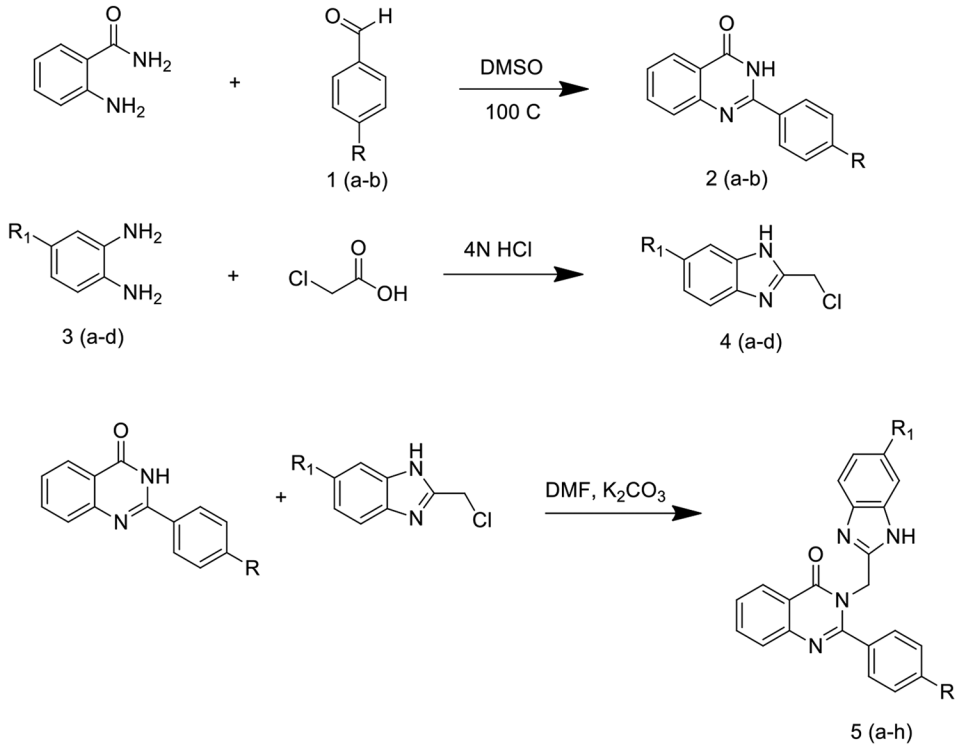


Figure 1: Reaction scheme for synthesis of Quinazolinone derivatives

added 250 ml of cold water, and precipitates produced were collected by filtration. To acquire derivatives of 2-phenylquinazolin-4(3*H*)-one 2(a-b), the compound was recrystallized in ethanol."

Procedure for the Preparation of Derivatives of 2-(chloromethyl)-1H-benzo[d]imidazole 4(a-d)

"0.1 mol of derivatives of *o*-phenylenediamine 3(a-d) and 0.1 mol of chloroacetic acid and 50 ml of 4 N hydrochloric acid were taken in a flask and the mixture was kept on a water bath and heated to reflux for 3 h. After that, the mixture was allowed to cool and then basified with ammonium hydroxide solution. The basification leads to the formation of precipitates which were separated by filtration and dried. Crude precipitates were recrystallized from methanol to give 2-(chloromethyl)-1*H*-benzo[d]imidazole derivatives 4(a-d)."[34]

Synthesis of 3-((1H-benzo[d]imidazol-2-yl)methyl)-2-phenylquinazolin-4(3H)-one Derivatives 5(a-h)

Two mmol of 2(a-b), 2 mmol of 4(a-d), 6 mmol K_2CO_3, and 20 ml of DMF were taken into a flask with flat bottom and were stirred magnetically for 18 h at room temperature. After that, poured water into flask to separate the solids. To get final product 5(a-h), the solids were filtered, recrystallized from hot ethanol, and dried.

Anticancer Studies on MCF-7 Cell Line

Anticancer activity was carried out at Skanda Life Sciences Pvt. Ltd., Bengaluru, India, using (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) (MTT) assay system. MTT is a salt of tetrazolium which is water soluble and on dissolution in salt solutions or media without phenol red, produces a yellowish-colored solution. This MTT method employs simple, precise, and repeatable process for measuring the living cells' activity using enzyme mitochondrial dehydrogenases. In sustainable cells, mitochondrial dehydrogenase enzymes cleave the tetrazolium ring of dissolved MTT, causing formation insoluble purple-colored formazan. The amount of formazan formed due to change in viable cell number directly relates to extent of effects produced by the test material.

Preparation of test solutions

Doxorubicin was chosen as the reference compound. Doxorubicin at a concentration of 10 mM was obtained and DMEM plain media was used to prepare 2-fold serial dilutions ranging 100 μM–3.125 μM. Similarly, a 10 mM stock of samples was prepared for cytotoxicity tests and DMEM plain media was used to prepare serial 2-fold dilutions ranging 100 μM–3.125 μM.

Culture medium and cell lines

"MCF-7 cell lines were procured from ATCC. DMEM supplemented with 10% inactivated fetal bovine serum (FBS), penicillin (100 IU/ml), and streptomycin (100 g/ml) was used to culture stock cell at 37°C in moistened atmosphere of 5% CO_2 until confluent. Cell disassociating solution (0.05% glucose in PBS, 0.02% EDTA, and 0.2% trypsin) was used to separate cells. Then, sustainability of the cells is confirmed before centrifugation. In addition, 50,000 cells/well were seeded in a 96-well plate and incubated in 5% CO_2 incubator for 24 h in a 37°C."[35]

Procedure

"Respective media containing 10% FBS was used to adjust cell count to 5.0×10^5 cells/ml after trypsinizing of monolayer cell culture. A 100 μl of the diluted cell suspension (50,000 cells/well) was added to each well of the 96-well microtiter plate. A partial monolayer was formed after 24 h. The supernatant liquid was removed and monolayer was washed once with the medium. A 100 μl of different test concentrations of test drugs were added on to the partial monolayer in microtiter plates. The plates were allowed to incubate in 5% CO_2 atmosphere at 37°C for 24 h. After incubation period is over, the test solution in wells was discarded and to each well, 100 μl of MTT (5 mg/10 ml of MTT in PBS) was added. The plates were further incubated in in 5% CO_2 atmosphere at 37°C for 4 h. After that again, supernatant liquid was removed and 100 μl of DMSO was added and the plates were gently stirred to solubilize the formed formazan. A microplate reader was used to measure absorbance at a wavelength of 590 nm. The percentage growth inhibition was calculated using the following formula.

$$\% \text{ Inhibition} = ((\text{OD of Control} - \text{OD of sample})/\text{OD of Control}) \times 100.$$

Moreover, concentration of test drug needed to inhibit cell growth by 50% (IC_{50}) values is generated from the dose-response curves for each cell line."[35]

Results and Discussion

Synthesis of Derivatives

Following the above procedure, a total of eight compounds were synthesized. Various methods were used to characterize the synthesized molecules, including M. pt., IR, and ^{1}H-NMR spectroscopy. The information presented here includes parameters such as color, melting point, yield (percentage yield), IR (in cm^{-1}), ^{1}H-NMR (400 MHz, DMSO-d6), and ^{13}C-NMR (100 MHz, DMSO-d6) δ data.

3-((1H-benzo[d]imidazol-2-yl)methyl)-2-phenylquinazolin-4(3H)-one (5a)

Color light yellow, M. Pt. 177–80°C, yield 0.55 g (78%), IR C-N 1210, C=C 1610, 1485, C=O 1710, C-H 2950, C-H Ar 3065, N-H 3310 and ^{1}H-NMR 5.03 (s, 2H), 7.22–7.12 (m, 2H), 7.53–7.42 (m, 5H), 7.60–7.53 (m, 1H), 7.64 (dd, J = 8.5, 1.2 Hz, 1H), 7.78 (ddd, J = 8.4, 7.0, 1.2 Hz, 1H), 8.16 (dd, J = 8.0, 1.3 Hz, 1H), 8.46–8.36 (m, 2H), 11.01 (s, 1H). ^{13}C-NMR 162.57, 155.42, 151.10, 148.05, 138.88, 136.48, 136.27, 134.50, 130.47, 129.20 (d, J = 9.5 Hz), 126.66, 126.43, 124.95, 122.30 (d, J = 6.9 Hz), 121.41, 116.63, 114.89, 42.34.

3-((6-chloro-1H-benzo[d]imidazol-2-yl)methyl)-2-phenylquinazolin-4(3H)-one (5b)

Color brown, M. Pt. 180–83°C, yield 0.56g (73%), IR C-Cl 670, C-N 1250, C=C 1615, 1480, C=O 1700, C-H 2980, C-H Ar 3080, N-H 3350 and ^{1}H-NMR 5.03 (s, 2H), 7.38 (dd, J = 8.2, 2.2 Hz, 1H), 7.55–7.43 (m, 4H), 7.59 (d, J = 2.2 Hz, 1H), 7.70–7.60 (m, 2H), 7.81 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 8.19 (dd, J = 8.0, 1.4 Hz, 1H), 8.48–8.39 (m, 2H), 11.17 (s, 1H). ^{13}C-NMR 165.23, 157.71, 150.71, 149.10, 138.64, 136.46 (d, J = 5.0 Hz), 135.46, 131.46, 130.25 (d, J = 9.5 Hz), 128.46, 127.65, 126.43, 125.75, 122.65, 122.41, 119.57, 113.90, 42.41.

3-((6-methoxy-1H-benzo[d]imidazol-2-yl)methyl)-2-phenylquinazolin-4(3H)-one (5c)

Color light brown, M. Pt. 170–73°C, yield 0.58g (80%), IR C-N 1245, C=C 1600,1470,C=O 1715,C-H 2900,C-H Ar 3080,N-H 3280 and ^{1}H-NMR 2.41 (d, J = 0.5 Hz, 3H), 5.03 (s, 2H), 7.28–7.20 (m, 1H), 7.40–7.30 (m, 2H), 7.65–7.53 (m, 4H), 7.64 (dd, J = 8.5, 1.2 Hz, 1H), 7.78 (ddd, J = 8.4, 7.0, 1.2 Hz, 1H), 8.18 (dd, J = 8.0, 1.3 Hz, 1H), 8.50–8.41 (m, 2H), 11.21 (s, 1H). ^{13}C-NMR 166.67, 155.42, 150.33, 149.06, 136.52 (d, J = 8.2 Hz), 135.17, 134.44 (d, J = 12.6 Hz), 130.47, 129.20 (d, J = 9.5 Hz), 126.66, 126.02, 125.05, 123.63, 122.44, 115.93, 113.55, 42.21, 21.36.

3-((6-nitro-1H-benzo[d]imidazol-2-yl)methyl)-2-phenylquinazolin-4(3H)-one (5d)

Color light orange, M. Pt. 242–45°C, yield 0.50 g (64%), IR C-N 1220, N=O 1550, C=C 1620, 1480, C=O 1705, C-H 2910, C-H Ar 3100, N-H 3300 and ^{1}H-NMR 5.03 (s, 2H), 7.55–7.44 (m, 4H), 7.64 (dd, J = 8.5, 1.2 Hz, 1H), 7.83–7.74 (m, 2H), 8.20 – 8.07 (m, 2H), 8.46–8.32 (m, 3H), 11.69 (s, 1H). ^{13}C-NMR 162.57, 156.32, 150.79, 148.75, 144.27, 142.46, 136.48, 136.13, 133.42, 131.84, 128.26 (d, J = 9.5 Hz), 127.68, 125.24, 123.93, 122.46, 118.51, 117.83, 109.55, 42.44.

3-((1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methoxyphenyl) quinazolin-4(3H)-one (5e)

Color light yellow, M. Pt. 229–32°C, 0.6 g (80%), IR: C-N 1100, C-O 1215, C=C 1605, 1460, C=O 1720, C-H 2950, C-H Ar 3000, N-H 3400 and ^{1}H-NMR 3.78 (s, 2H), 5.05 (s, 1H), 7.03–6.99 (m, 2H), 7.25–7.13 (m, 2H), 7.57–7.42 (m, 2H), 7.68–7.52 (m, 1H), 7.65 (dd, J = 8.5, 1.2 Hz, 1H), 7.77 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 8.19 (dd, J = 8.0, 1.3 Hz, 1H), 8.38–8.26 (m, 2H), 11.09 (s, 1H). ^{13}C-NMR 162.65, 160.63, 155.17, 152.21, 148.06, 140.26, 135.97, 135.12, 130.93 (d, J = 15.8 Hz), 127.49, 126.43, 125.05, 121.90 (d, J = 6.9 Hz), 120.91, 117.07, 115.99, 114.51, 55.35, 43.43.

3-((6-chloro-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methoxyphenyl)quinazolin-4(3H)-one(5f)

Color brown, M. Pt. 235–38°C, 0.58g (70%), IR C-Cl 685, C-N 1180, C-O 1050, C=C 1600, 1480, C=O 1714, C-H 2965, C-H Ar 3095, N-H 3380 and ^{1}H-NMR 3.68 (s, 3H), 5.02 (s, 2H), 7.02 – 6.86 (m, 2H), 7.38 (dd, J = 8.2, 2.2 Hz, 1H), 7.50 (ddd, J = 8.4, 7.09, 1.3 Hz, 1H), 7.75–7.66 (m, 3H), 7.78 (ddd, J = 8.4, 7.0, 1.19 Hz, 1H), 8.17 (dd, J = 8.0, 1.3 Hz, 1H), 8.34–8.22 (m, 2H), 11.17 (s, 1H). ^{13}C-NMR 164.27, 163.45, 157.67, 152.71, 150.78, 140.63, 138.33, 136.31, 132.42 (d, J = 16 Hz), 130.45, 128.51, 128.12, 126.22, 124.55, 123.11, 121.96, 116.55, 115.69, 57.13, 44.64.

3-((6-methoxy-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methoxyphenyl)quinazolin-4(3H)-one (5g)

Color yellow-brown, M. Pt. 181–84°C, 0.45g (57%), IR C-N 1330, C-O 1275, C=C 1605, 1480, C=O 1730, C - H 2895, C - H Ar 3150, N-H 3450 and ^{1}H-NMR 2.41 (d, J = 0.5 Hz, 3H), 3.79 (s, 3H), 5.13 (s, 2H), 7.03–6.99 (m, 2H), 7.29–7.21 (m, 1H), 7.45–7.35 (m, 2H), 7.49 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.65 (dd, J = 8.5, 1.2 Hz, 1H), 7.80 (ddd, J = 8.4, 7.0, 1.2 Hz, 1H), 8.15 (dd, J = 8.0, 1.3 Hz, 1H), 8.36–8.24 (m, 2H), 11.25 (s, 1H). ^{13}C-NMR 163.07, 162.93, 156.67, 151.63, 147.56, 138.08, 136.68, 134.44 (d, J = 12.6 Hz), 130.93 (d, J = 15.8 Hz), 128.16, 127.42, 126.41, 125.13, 122.91, 117.43, 116.02, 115.05, 56.82, 43.91, 22.86.

2-(4-methoxyphenyl)-3-((6-nitro-1H-benzo[d]imidazol-2-yl) methyl)quinazolin-4(3H)-one(5h)

Color orange, M. Pt. 247–50°C, 0.46 (55%), IR C-N 1305, N=O 1530, C=C 1600, 1470, C=O 1717, C-H 2910, C-H Ar 3135, N-H 3410 and ^{1}H-NMR 3.81 (s, 3H), 5.57 (s, 2H), 7.05–6.98 (m, 2H), 7.52 (ddd, J = 8.2, 7.1, 1.3 Hz, 1H), 7.65 (dd, J = 8.5, 1.2 Hz, 1H), 7.84–7.76(m, 2H),

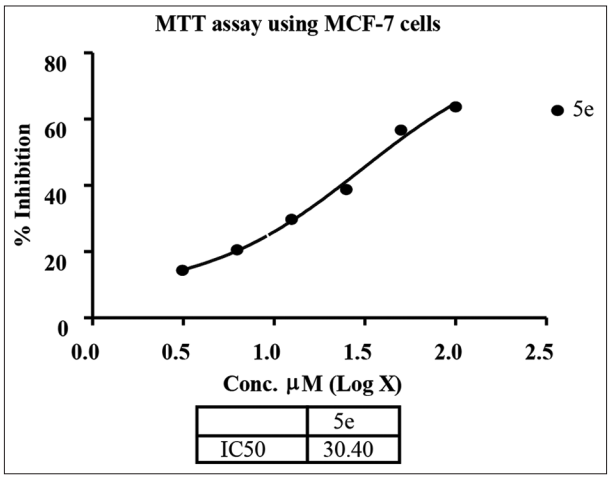


Figure 2: IC_{50} value of compound 5e

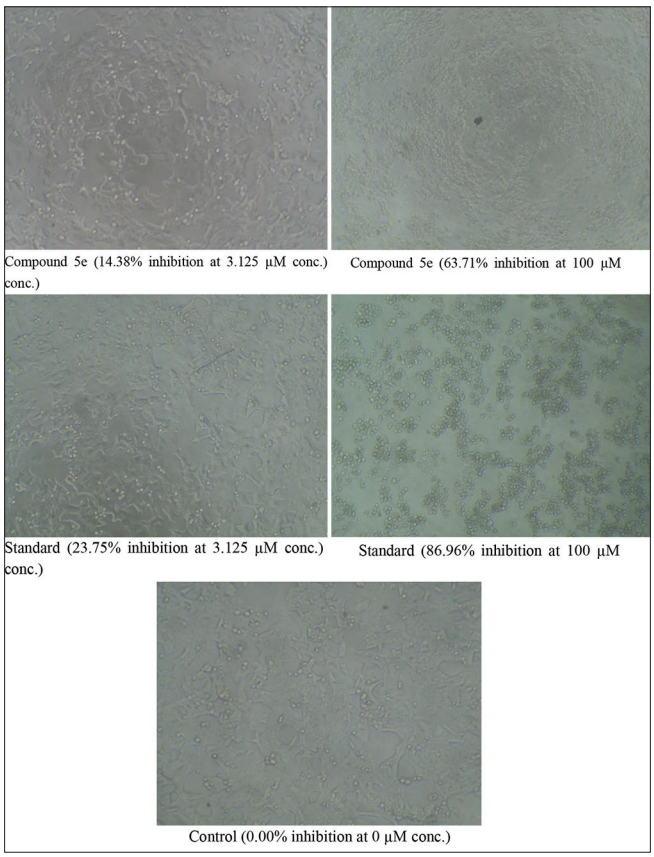


Figure 3: % inhibition of MCF-7 cell lines by compound 5e, Standard (doxorubicin) and control

Table 2: Anti-cancer activity of synthesized compounds

Sample	*Control*				*5a*						*5b*		
Conc. in µM	0	3.125	6.25	12.5	25	50	100	3.125	6.25	12.5	25	50	100
OD @ 590 nm	0.598	0.574	0.554	0.521	0.489	0.451	0.426	0.588	0.568	0.546	0.52	0.489	0.456
% inhibition	0	4.01	7.36	12.88	18.23	24.58	28.76	1.67	5.02	8.7	13.04	18.23	23.75
IC50 in µM					-						-		
Sample	*Control*				*5c*						*5d*		
Conc. in µM	0	3.125	6.25	12.5	25	50	100	3.125	6.25	12.5	25	50	100
OD @ 590 nm	0.598	0.592	0.568	0.544	0.51	0.477	0.423	0.577	0.556	0.531	0.489	0.445	0.389
% inhibition	0	1	5.02	9.03	14.72	20.23	29.26	3.51	7.02	11.2	18.23	25.59	34.95
IC50 in µM					-						-		
Sample	*Control*				*5e*						*5f*		
Conc. in µM	0	3.125	6.25	12.5	25	50	100	3.125	6.25	12.5	25	50	100
OD @ 590 nm	0.598	0.512	0.475	0.42	0.366	0.259	0.217	0.578	0.554	0.523	0.498	0.425	0.4
% inhibition	0	14.38	20.57	29.77	38.8	56.69	63.71	3.34	7.36	12.54	16.72	28.93	33.11
IC50 in µM					-						-		
Sample	*Control*				*5g*						*5h*		
Conc. in µM	0	3.125	6.25	12.5	25	50	100	3.125	6.25	12.5	25	50	100
OD @ 590 nm	0.598	0.567	0.524	0.487	0.444	0.385	0.326	0.574	0.558	0.52	0.466	0.41	0.374
% inhibition	0	5.18	12.37	18.56	25.75	35.62	45.48	4.01	6.69	13.04	22.07	31.44	37.46
IC50 in µM					-								
Sample	*Control*				*Doxorubicin*								
Conc. in µM	0	3.125	6.25	12.5	25	50	100						
OD @ 590 nm	0.598	0.456	0.387	0.317	0.245	0.137	0.078						
% inhibition	0	23.75	35.28	46.99	59.03	77.12	86.96						
IC50 in µM					22.17								

8.21–8.08 (m, 2H), 8.38–8.27 (m, 3H), 11.69 (s, 1H). ^{13}C-NMR 163.67, 162.54, 156.28, 151.90, 149.16, 145.38, 143.57, 137.24, 135.61, 132.04 (d, J = 16.1 Hz), 127.75, 127.45, 126.05, 122.52, 119.62, 118.93, 115.62, 110.31, 56.45, 43.54.

Anticancer Activity

Using the MTT assay means and doxorubicin as a reference drug, all compounds synthesized were tested on MCF-7 cell for anticancer activity. All synthesized compounds demonstrated modest activity, but compound 5e demonstrated good activity with 63.71% inhibition at 100 µM (IC_{50} = 30.4) in comparison to 86.96% inhibition by doxorubicin (IC_{50} = 22.17) [Figures 2 and 3]. The detail data of % inhibition of MCF-7 cell lines by reported compounds are given in Table 2.

Conclusion

A sequence of eight compounds with quinazolinone nucleus was prepared and confirmed using techniques like as melting point, IR, proton NMR, and ^{13}C-NMR. The anticancer ability of compounds 5(a-h) was measured against MCF-7 cell lines, and one of the compounds, 5e, demonstrated good anticancer activity as compared to doxorubicin, with IC_{50} values of 30.4 and 22.17, respectively.

Acknowledgments

The authors are grateful to the administration of ASBASJSM College of Pharmacy, Bela, for all backing and amenities.

References

1. Mahdy HA, Ibrahim M, Metwaly A, Belal A, Mehany AB, El-Gamal KM, *et al*. Design, synthesis, molecular modeling, *in vivo* studies and anticancer evaluation of quinazolin-4(3H)-one derivatives as potential VEGFR-2 inhibitors and apoptosis inducers. Bioorg Chem 2020;94:103422.
2. Cancer. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer. [Last accessed on 2020 Nov 26].
3. Gatadi S, Pulivendala G, Gour J, Malasala S, Bujji S, Parupalli R, *et al*. Synthesis and evaluation of new 4 (3H)-quinazolinone derivatives as potential anticancer agents. J Mol Struct 2020;1200:127097.
4. Rakesh KP, Kumara HK, Manukumar HM, Channe Gowda D. Anticancer and DNA binding studies of potential amino acids based quinazolinone analogs: Synthesis, SAR and molecular docking. Bioorg Chem 2019;87:252-64.
5. Hudson L, Mui J, Vázquez S, Carvalho DM, Williams E, Jones C, *et al*. Novel quinazolinone inhibitors of ALK2 flip between alternate binding modes: Structure-activity relationship, structural characterization, kinase profiling, and cellular proof of concept. J Med Chem 2018;61:7261-72.
6. Hekal MH, Abu El-Azm FS. New potential antitumor quinazolinones derived from dynamic 2-undecyl benzoxazinone: Synthesis and cytotoxic evaluation. Synth Commun 2018;48:2391-402.
7. Liu HW, Liu HY, Li W, Zhang S, Wu Z, Li X, *et al*. CHEMISTRY design, synthesis, antiproliferative and antibacterial evaluation of quinazolinone derivatives. Med Chem Res 2019;28:8.
8. Venkatesh P, Tiwari VS. Design and synthesis of quinazolinone, benzothiazole derivatives bearing guanidinopropanoic acid moiety and their Schiff bases as cytotoxic and antimicrobial agents. Arab J Chem 2016;9:S914-25.
9. Gali R, Banothu J, Porika M, Velpula R, Hnamte S, Bavantula R, *et al*. Indolylmethylene benzo[h]thiazolo[2,3-b]quinazolinones: Synthesis, characterization and evaluation of anticancer and antimicrobial activities. Bioorg Med Chem Lett 2014;24:4239-42.
10. Nagamallu R, Srinivasan B, Ningappa MB, Kariyappa AK. Synthesis of novel coumarin appended bis(formylpyrazole) derivatives: Studies on their antimicrobial and antioxidant activities. Bioorg Med Chem Lett 2016;26:690-4.
11. Suresha GP, Suhas R, Kapfo W, Channe Gowda D. Urea/thiourea derivatives of quinazolinone-lysine conjugates: Synthesis and structure-activity relationships of a new series of antimicrobials. Eur J Med Chem 2011;46:2530-40.
12. Nanthakumar R, Muthumani P, Girija K. Anti-inflammatory and antibacterial activity study of some novel quinazolinones. Arab J

Chem 2014;7:1049-54.
13. Poojari S, Naik PP, Krishnamurthy G, Kumara KS, Sunil Kumar N, Naik S, *et al*. Anti-inflammatory, antibacterial and molecular docking studies of novel spiro-piperidine quinazolinone derivatives. J Taibah Univ Sci 2017;11:497-511.
14. Abdel-Aziz AA, Abou-Zeid LA, ElTahir KE, Ayyad RR, El-Sayed MA, El-Azab AS, *et al*. Synthesis, anti-inflammatory, analgesic, COX-1/2 inhibitory activities and molecular docking studies of substituted 2-mercapto-4(3 H)-quinazolinones. Eur J Med Chem 2016;121:410-21.
15. Rakesh KP, Manukumar HM, Gowda DC. Schiff's bases of quinazolinone derivatives: Synthesis and SAR studies of a novel series of potential anti-inflammatory and antioxidants. Bioorg Med Chem Lett 2015;25:1072-7.
16. Wang Z, Wang M, Yao X, Li Y, Tan J, Wang L, *et al*. Design, synthesis and antiviral activity of novel quinazolinones. Eur J Med Chem 2012;53:275-82.
17. Brown CE, Kong T, McNulty J, D'Aiuto L, Williamson K, McClain L, *et al*. Discovery of potent antiviral (HSV-1) quinazolinones and initial structure-activity relationship studies. Bioorg Med Chem Lett 2017;27:4601-5.
18. Kumar KS, Ganguly S, Veerasamy R, De Clercq E. Synthesis, antiviral activity and cytotoxicity evaluation of Schiff bases of some 2-phenyl quinazoline-4(3)H-ones. Eur J Med Chem 2010;45:5474-9.
19. Abdel-Aziz AA, Abou-Zeid LA, ElTahir KE, Mohamed MA, El-Enin MA, El-Azab AS, *et al*. Design, synthesis of 2,3-disubstitued 4(3H)-quinazolinone derivatives as anti-inflammatory and analgesic agents: COX-1/2 inhibitory activities and molecular docking studies. Bioorg Med Chem 2016;24:3818-28.
20. Aly MM, Mohamed YA, El-Bayouki KA, Basyouni WM, Abbas SY. Synthesis of some new 4(3H)-quinazolinone-2-carboxaldehyde thiosemicarbazones and their metal complexes and a study on their anticonvulsant,analgesic,cytotoxic and antimicrobial activities e Part-1. Eur J Med Chem 2010;45:3365-73.
21. Abdel-aziz AA, Bayomi SM, El-Sherbeny MA, Abdel-Aziz NI, ElTahir KE, Shehatou GS, *et al*. Synthesis, anti-inflammatory and analgesic agents : COX-1/2 inhibitory activities and molecular docking studies. Bioorg Med Chem 2016;24;3818-28.
22. Ram VJ, Tripathi BK, Srivastava AK. Synthesis and antihyperglycemic activity of suitably functionalized 3H-quinazolin-4-ones. Bioorg Med Chem 2003;11:2439-44.
23. Wei M, Chai WM, Wang R, Yang Q, Deng Z, Peng Y, *et al*. Quinazolinone derivatives: Synthesis and comparison of inhibitory mechanisms on α-glucosidase. Bioorg Med Chem 2017;25:1303-8.
24. Malanias MS, Millen J. Quinazolineacetic acids and related analogues as aldose reductase inhibitors. J Med Chem 1991;34:1492-503.
25. Mahajan PG, Dige N, Vanjare BD, Raza H, Hassan M, Seo SY, *et al*. Facile synthesis of new quinazolinone benzamides as potent tyrosinase inhibitors : Comparative spectroscopic and molecular docking studies. J Mol Struct 2019;1198:126915.
26. El-Azab AS, Eltahir KE. Synthesis and anticonvulsant evaluation of some new 2,3,8-trisubstituted-4(3H)-quinazoline derivatives. Bioorg Med Chem Lett 2012;22:327-33.
27. Al-Salem HS, Hegazy GH, El-Taher KE, El-Messery SM, Al-Obaid AM, El-Subbagh HI, *et al*. Synthesis, anticonvulsant activity and molecular modeling study of some new hydrazinecarbothioamide, benzenesulfonohydrazide, and phenacylacetohydrazide analogues of 4(3H)-quinazolinone. Bioorg Med Chem Lett 2015;25:1490-9.
28. Gawad NM, Georgey HH, Youssef RM, Sayed NA. Design, synthesis, and anticonvulsant activity of novel quinazolinone analogues. Med Chem Res 2011;20:1280-6.
29. Patel HM, Noolvi MN, Shirkhedkar AA, Kulkarni AD, Pardeshia CV, Suranaa SJ. Anti-convulsant potential of quinazolinones. RSC Adv 2016;6:44435-55.
30. Le Y, Gan Y, Fu Y, Liu J, Li W, Zou X, *et al*. Design, synthesis and *in vitro* biological evaluation of quinazolinone derivatives as EGFR inhibitors for antitumor treatment. J Enzyme Inhib Med Chem 2020;35:555-64.
31. Sabry MA, Ewida HA, Hassan GS, Ghaly MA, El-Subbagh HI. Synthesis, antitumor testing and molecular modeling study of some new 6-substituted amido, azo or thioureido-quinazolin-4(3H)-ones. Bioorg Chem 2019;88:102923.
32. Shao J, Fang Y, Zhao R, Chen F, Yang M, Jiang J, *et al*. Evolution from small molecule to nano-drug delivery systems: An emerging approach for cancer therapy of ursolic acid. Asian J Pharm Sci 2020;15:685-700.
33. Kim NY, Cheon CH. Synthesis of quinazolinones from anthranilamides and aldehydes via metal-free aerobic oxidation in DMSO. Tetrahedron Lett 2014;55:2340-4.
34. Kaur H, Singh B. Synthesis, characterisation and biological evaluation of substituted 4-((1H-Benzo[d]Imidazol-2-YL)Methoxy) coumarin derivatives as antimicrobial Agents. Indian J Pharm Biol Res 2019;7:1-8.
35. Bais S, Patel NJ. *In vitro* anti diabetic and anti obesity effect of *J. communis* extract on 3T3L1 mouse adipocytes: A possible role of MAPK/ERK activation. Obes Med 2020;18:100219.