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Synthesis and Anti-Cancer Activity of Novel Oxadiazole Quinazoline Analogues

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Abstract

Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have triggered established issues due to their extensively and distinct biopharmaceutical sports. Quinazoline derivatives encompass a huge spectrum of pharmaceutical hobby profile inclusive of antitumor, anti-HIV, antimicrobial, antibacterial, anti-inflammatory, CNS activity and cardiovascular activity. The overall goal of this study is to look at ways to increase efficient artificial techniques for the synthesis of oxadiazole substituted quinazoline analogues. Based on in silico research, ten analogues have been taken for wet lab synthesis. The synthesized compounds were screened for anticancer activity. The systems of the synthesized compounds were characterized by way of FT-IR, 1H NMR and MASS spectroscopy.

Keywords
Anticancer activity, Schrodinger, FT-IR

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INTRODUCTION:

Heterocyclic chemistry is a chemistry involving the heterocyclic compounds, which has atoms of at least two different elements as number of ring. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. 4(3H)-Quinazolinones and related quinazolines are classes of fused heterocyclic that are of considerable interest because of the diverse range of their biological properties, for example anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities [1-6]. Quinazoline pharmacophore has been selected for drug design because of great importance in their biological as well as synthetic approach of medicinal chemistry. Though the parent quinazoline molecule is rarely mentioned by itself in technical literature, substituted derivatives have been synthesized for medicinal purposes such as anti -malarial, anti - cancer and anti- bacterial agents. Quinazoline substituted oxadiazole derivatives were designed for anti-bacterial activities based on multi target drug design approach. For anti- bacterial studies, the target proteins selected were DNA gyrase and β-ketoacyl-acyl carrier protein synthase III (FabH). Molecular docking studies were supported to synthesize novel quinazoline derivatives which target more than one receptor for the same activity in order to increase their pharmacological efficacy [7-9].

MATERIALS AND METHODS:

All the reagents and solvents used were of analytical or synthetic grade and obtained from commercial sources. The newly synthesized compounds were characterized by Melting point, IR, 1HNMR and Mass spectral analysis. The melting points of the synthesized analogues were determined with an electro thermal melting point apparatus. The purity

of the compounds were ascertained by TLC over precoated, pre-activated glass plates with solvent system ethyl acetate: petroleum ether (3:7). Purity of the compounds was confirmed by single spot in TLC and consistency in the Rf value. FT-IR spectra of the synthesized compounds were recorded using KBr pellets in the range of 4000-500cm-1 on Agilent Cary 630 FTIR spectrometer, at College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram. NMR spectra of compounds were recorded on Bruker Avance AV 500 NMR spectrometer at 500 MHz, at National Institute for Interdisciplinary Science and Technology (NIIST), Council of Scientific and Industrial Research (CSIR), Govt. of India, Thiruvananthapuram. Mass spectra (LC-MS) were recorded by thermo executive orbitrap FTMS instrument in Department of Applied Chemistry, CUSAT, Kochi.

Synthetic procedure

Step 1. Synthesis of 2-phenyl-2, 3-dihydroquinazolin -4(1H)-one

A mixture of anthranilamide (1 mmol), benzaldehyde (1 mmol) and ammonium chloride (5mol %) in 20 ml ethanol was refluxed at 120 °C for 15 minutes. The progress of the reaction was monitored by TLC (ethyl acetate/ n- hexane). After completion of the reaction, a solid was obtained. It was washed with water and recrystallized from ethanol**.** TLC was performed by using mobile phase-ethyl acetate: petroleum ether (3:7), Rf value 0.68, yield 85%, m.p 197° C.

Step 2. Synthesis of ethyl [(2-phenyl-1, 2-dihydroqui nazolin-4-yl) oxy] acetate

In 500 ml round bottom flask, take 15-20 ml dry DMF (dimethyl formamide). To this add 2-methyl 2, 3-dihydroquoinazolinone (0.01 mol, 1.6 g) and ethyl chloroacetate (0.01 mol, 1.25 ml) and anhydrous potassium carbonate (0.1 mol, 1.38 g). The resultant mixture was stirred and refluxed for 9-10 hours at 80°C. After completion of the reaction, the reaction mixture was filtered and poured into large amount of water. The solid separated was filtered and washed with water, the solid was dried and recrystallized from ethanol. TLC; mobile phase-ethyl acetate: petroleum ether (3:7), Rf value 0.63, yield 82%, m.p 183°C.

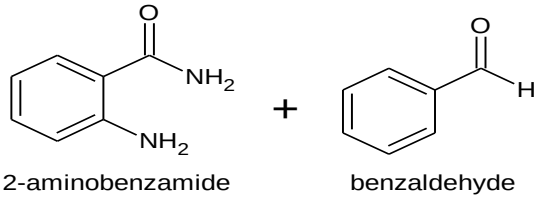
Step 3. Synthesis of 2-[(2-phenyl-1, 2-dihydroqui nazolin-4-yl] oxy) acetohydrazide

Compound 2(0.01mol) and hydrazine hydrate (0.01mol, 0.9ml) in ethanol(20ml) were placed in round bottom flask and microwave irradiated (350W, 76-78°C) for 3.5 min. After completion of reaction (monitored by TLC), the mixture was cooled and the resulting solid was filtered, dried and recrystallized from ethanol. TLC; mobile phase-ethyl acetate: petroleum ether (3:7), Rf value 0.55, Yield 80%, MP 175°C.

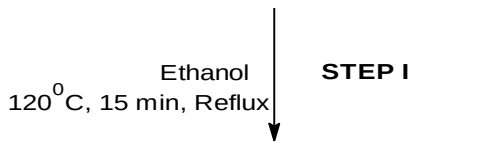
Step 4. Synthesis of 2- [(2-phenyl-1, 2-dihydroquina zolin-4-yl) oxy]-N-[(E)-phenyl methylidene] aceto hydrazide

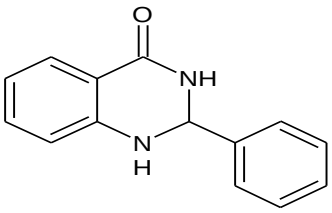
A mixture of compound 3 (0.01mol), aromatic aldehyde (0.01 mol) and 2-3 drops of glacial acetic acid in ethanol (20ml) were placed in round bottom flask and microwave irradiated (400W, 76-78°C) for 3 minute. After completion of the reaction, the solvent was removed and residue recrystallized from ethanol.

SCHEME



2-aminobenzamide benzaldehyde

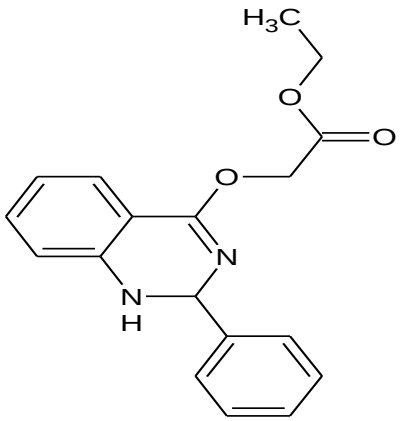




2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one

$ClCH_2COOC_2H_5$, DMF
80^0C, 9-10 hrs, stirr & Reflux

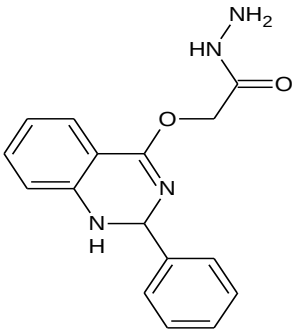
STEP 2



ethyl [(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetate

$NH_2NH_2.H_2O$
EtOH
Reflux for 5hrs

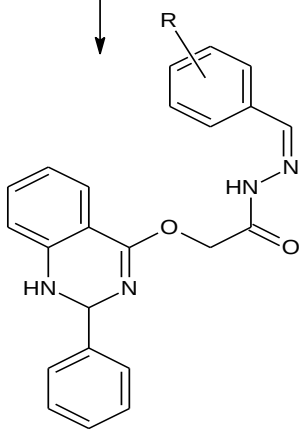
STEP 3



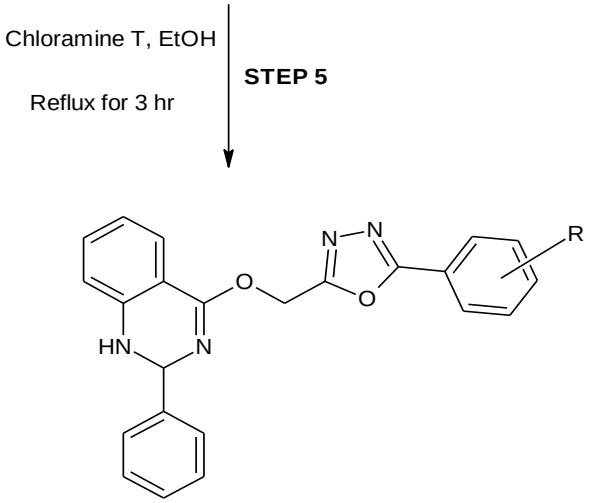
2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide

ArCHO, EtOH
MW, 400 W,76-78^{0}C, 3 min

STEP 4



2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]-*N*'-[(*Z*)-phenylmethylidene]acetohydrazide



2-phenyl-4-[(5-phenyl-1,3,4-oxadiazol-2-yl)methoxy]-1,2-dihydroquinazoline

- Recrystallization solvent-ethanol
- TLC; mobile phase-ethyl acetate: petroleum ether(3:7)

General procedure was adapted for the synthesis of all analogues and thus following compounds are synthesized,

➢ **QS-1**:2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy] -*N*'-[(*E*)phenylmethylidene] acetohydrazide

Aldehyde: ***benzaldehyd***e; MW Irradiation (400W, 78°C, 3 minute).

➢ **QS-2**: N'-[(E)- (4-chlorophenyl) methylidene]- 2-[(2-phenyl-1, 2-dihydroquinazolin-4-yl)oxy] acetohydrazide

Aldehyde: ***P- Chlorobenzaldehyde***; MW Irradiation (400W, 78°C 3 min)

➢ **QS-3**:*N*'-[(*E*)-(4-bromophenyl)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide

Aldehyde:***P-Bromobenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).

➢ **QS-4**:*N*'-[(*E*)-(4-hydroxy phenyl)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide

Aldehyde: ***P-hydroxybenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).

➢ **QS-5**:*N*'-[(*E*)-(4-nitrophenyl)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide

Aldehyde: ***4-nitrobenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).

➢ **QS-6**:*N*'-[(*E*)-(3-nitrophenyl)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide

Aldehyde: ***3-nitrobenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).

➢ **QS-7**:*N*'-[(*E*)-(2-methoxyphenyl)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide

Aldehyde: ***2-methoxybenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).

➢ **QS-8** :*N*'-[(*E*)-(4-aminophenyl)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide

Aldehyde: ***P-aminobenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).

➢ **QS-9**:*N*'-[(*E*)-(2-hydroxyphenyl)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide

Aldehyde: ***Salicylaldehyde***; MW Irradiation (400W, 78°C, 3 minute).

➢ **QS-10**:*N*'-[(*E*)-(4-dimethylamino)methylidene]-2-[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]acetohydrazide

Aldehyde: ***P-dimethylaminobenzaldehyde***; MW Irradiation (400W, 78°C, 3 minute).

Step 5. Synthesis of 2-phenyl-4-[(5-phenyl-1, 3, 4-oxadiazol-2-yl) methoxy]-1, 2-dihydroquinazoline

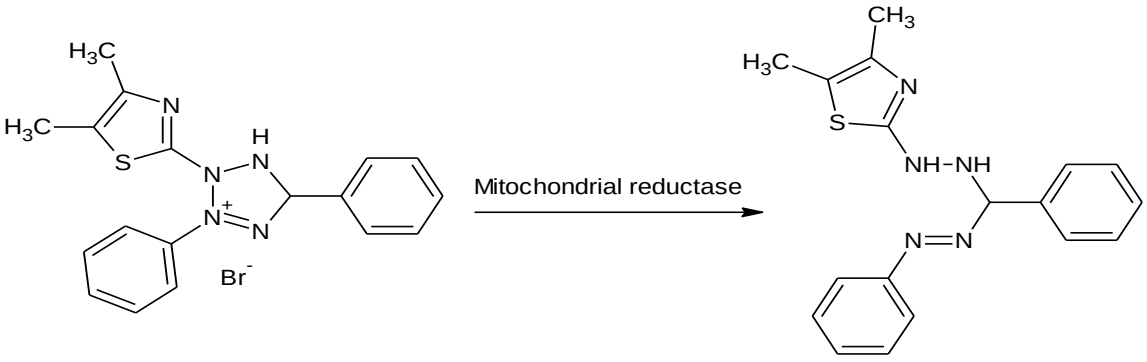
To a solution of compound 4 (schiff base) (0.01mol) and chloramine T (0.05 mol) in ethanol (20ml) was refluxed for 3 hour. After completion of the reaction, it was filtered to remove sodium chloride. The filtrate along with washings was concentrated to a small volume and left at room temperature. A solid mass so obtained was filtered and crystallised from ethanol to yield oxadiazole substituted quinazoline derivatives (QO).

5.3.2 ANTICANCER ACTIVITY

The anticancer activity of selected synthesized derivatives were measured by using MTT assay on cultured HCT 116 cell lines. The MTT Cell Proliferation Assay measures the cell proliferation rate and conversely, when metabolic events lead to apoptosis or necrosis, the reduction in cell viability. The screening was carried out at College Of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram.

Principle

The MTT cell proliferation assay is a quantitative colorimetric method to determine the cell proliferation. It utilizes the yellow tetrazolium salt (3-(4, 5- dimethylthiazol-2-yl)-2, 5- diphenyltetrazoli um- bromide) which is metabolized by mitochondrial succinic dehydrogenase activity of proliferating cells to yield a purple formazan product by the mitochondria of viable cell. The MTT reagent is kept at 4°Cin the dark. The cells are then solubilized with an organic solvent (Eg: Dimethyl sulfoxide) and the released, solubilized formazan reagent is measured spectrophotometrically at 540 nm. Since reduction of MTT can only occur in metabolically active cells, the level of activity is a measure of the viability of the cells.



3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazonium bromide (**MTT**

(E, Z)-5-(4, 5-dimethyl thiazol-2-yl) -1, 3-diphenyl formazan **(Formazan)**

Protocol

Short 96 well assay: each condition should be done in triplicate or more.

- **DAY ONE**: Trypsinize one T-25 flask and add 5 ml of complete media to trypsinized cells. Centrifuge in a sterile 15 ml falcon tube at 500 rpm in the swinging bucked rotor (~400 x g) for 5 min.
- Remove media and resuspend cells to 1.0 ml with complete media.
- Count and record cells per ml. Remember to remove the cells aseptically when counting.
- DILUTE the cells to 75,000 cells per ml. Use complete media to dilute cells.
- Add 100 µl of cells (7500 total cells) into each well and incubate overnight.
- **DAY TWO**: Treat cells on day two with agonist, inhibitor or drug.

  - If removing media, do very carefully. This is where most variation in Data may occur.
  - Final volume should be 100µl per well.
- **DAY THREE**: Add 20µl of 5 mg/ml MTT to each well. Include one set of wells with MTT but no cells (control). All should be done aseptically.
- Incubate for 3.5 hours at 37ºC in culture hood.
- CAREFULLY Remove media. Do not disturb cells and do not rinse with PBS.
- Add 150 µl MTT solvent.
- Cover with tinfoil and agitate cells on orbital shaker for 15 min.

- Read absorbance at 590 nm with a reference filter of 620 nm

Procedure

HCT 116 (Human colon cancer) cell lines were cultured in DMEM supplemented with 10 % fetal bovine serum (FBS), 100µg/ml streptomycin and 100 units/ml penicillin G at 37ºC in a 5% CO_2 incubator. After attaining 90 % confluency the cells were detached with 0.05 % trypsin/EDTA. Then the cells were seeded in 96 well microtitre plate (200µl/well) with concentration of 2×10^3 cells/cm^2. When the cultivated cells attained 40-50 % confluency, the cells were exposed to various concentrations of 5-FU and selected derivatives prepared in 1 % DMSO and sterile water and then incubated for 48 hours at 37 ºC in a 5 % CO_2 incubator. In negative control, the cells were co-treated with vehicle and untreated HCT-116 cells were used as a cell line control. After the incubation for 48 hours, the cells were washed with PBS then added 20 µl MTT solution was added to all test and control wells, the plate was gently shaken well, then incubated at 37 ºC in a humidified 5 % CO_2 incubator for 3 hours. When the purple colour of the formazan was clearly visible through the inverted microscope, MTT solution was removed and added 200 µl of DMSO. The wells were mixed gently by pipetting up and down in order to solubilize the formazan crystals. The plate was incubated for 30 min in a dark area at room temperature until the cells were lysed and obtained a purple colour. The optical density was taken at 540 nm using microplate reader (Bio-TekPower Wave XS) [67, 68]

Calculation

From the absorbance reading from each well, the growth of tumoral cells and viability of the cells were determined using the formula:

$$\text{Percentage viability (\%)} = \frac{\text{OD of test}}{\text{OD of control}} \times 100$$

Data interpretation [69]

The plot of data obtained from the procedure (MTT Assay for Determination of Cell number to be used) should provide a curve that has a linear portion. Selection of a cell number that falls within the linear portion of the curve (i.e. providing values between the range of 0.75 and 1.25) allows for the measurement of both stimulation and inhibition of cell proliferation.

If the absorbance values of the experimental samples are higher than the negative control cells, this indicates an increase in cell proliferation. Alternatively, if the absorbance rates of the experimental samples are lower than the negative controls, this indicates a reduction in the rate of cell proliferation or a reduction in overall cell viability.

RESULTS AND DISCUSSIONS:

The *in-silico* molecular modelling studies of oxadiazole substituted quinazoline analogues were carried out successfully with the aid of different software for selection of suitable drug candidates prior to wet lab synthesis. *In-silico* studies were performed on 15 analogues by means of ACD Lab Chemsketch 12.0, ChemDraw, Molinspiration, PASS, and Schrodinger. Out of 15 proposed analogues, 10 candidates were chosen for wet lab synthesis. The synthesized analogues were characterized by FT-IR, 1H NMR and MASS spectral analysis. All the proposed analogues were subjected to flexible docking using GLIDE XP (Extra Precision) on EGFR Tyrosine kinase (2ITY) and Human androgen receptor ligand binding domain (20Z7) which indicates the anticancer activity.

CONCLUSION:

The present work involved in the preliminary *In-silico* screening of quinazoline analogues, for quantifying their molecular descriptors using computational software. Molecular docking was performed for ten analogues using Schrodinger Maestro and multi targeting drug design was carried out by choosing two proteins for anticancer activity. The proteins selected were EGFR Tyrosine kinase (2ITY) and Human androgen receptor ligand binding domain (20Z7). All analogues showed good protein interactions.

The compounds were selected for the wet lab synthesis on the basis of desired physicochemical properties, obeying Lipinski Rule of five and good docking score. Ten analogues were synthesized by both conventional and microwave method and the purity of synthesized analogues were ascertained by consistency in melting point and R_f value. The compounds were characterized by IR, ^{1}H NMR and Mass spectral analysis.

Four compounds (QO-1, QO-4, QO-5 and QO-6) were studied for cytotoxicity studies against HCT 116 human colon cancer cell lines using MTT assay. Among these compounds, QO-4 showed better activity at the concentration of 100µg/ml.

Table 1. Characterization of step 4 product

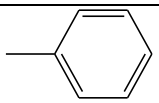
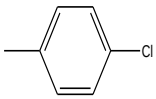
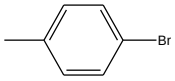
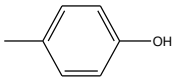
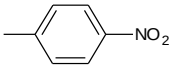
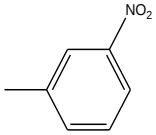
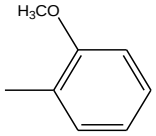
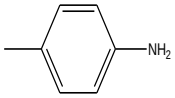
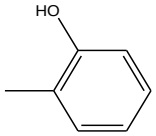
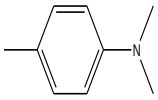
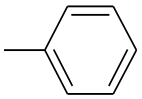
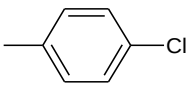
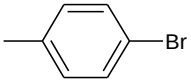
Compound code	R	Molecular formula	Molecular weight	Melting point	% yield	R_f
QS-1		$C_{23}H_{20}N_4O_2$	384.43	176°C	68	0.55
QS-2		$C_{23}H_{19}ClN_4O_2$	418.87	173°C	65	0.58
QS-3		$C_{23}H_{19}BrN_4O_2$	463.32	171°C	63	0.56
QS-4		$C_{23}H_{20}N_4O_3$	400.42	168°C	69	0.41
QS-5		$C_{23}H_{19}N_5O_4$	429.42	175°C	70	0.49
QS-6		$C_{23}H_{19}N_5O_4$	429.42	169°C	66	0.40
QS-7		$C_{24}H_{22}N_4O_3$	414.45	164°C	62	0.44
QS-8		$C_{23}H_{21}N_5O_2$	399.44	165°C	66	0.46
QS-9		$C_{23}H_{20}N_4O_3$	400.42	167°C	71	0.43
QS-10		$C_{25}H_{25}N_5O_2$	427.49	172°C	73	0.50

Table 2. Characterization of oxadiazole-quinazoline analogues

Compound code	R	Molecular formula	Molecular weight	Melting point	% yield	R_f value
QO-1		$C_{23}H_{18}N_4O_2$	382.41	82°C	62	0.45
QO-2		$C_{23}H_{17}ClN_4O$	416.85	71°C	60	0.43
QO-3		$C_{23}H_{17}BrN_4O$	461.31	94°C	67	0.42

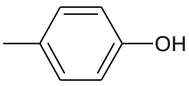
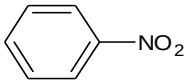
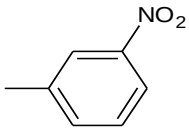
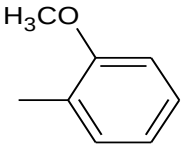
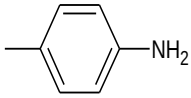
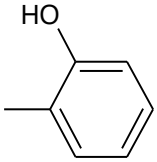
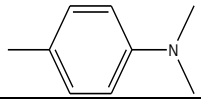
QO-4		$C_{23}H_{18}N_4O_3$	398.41	75°C	69	0.26
QO-5		$C_{23}H_{17}N_5O_4$	427.41	95°C	72	0.39
QO-6		$C_{23}H_{17}N_5O_4$	427.41	97°C	64	0.45
QO-7		$C_{24}H_{20}N_4O_3$	412.44	95°C	73	0.38
QO-8		$C_{23}H_{19}N_5O_2$	397.42	85°C	67	0.44
QO-9		$C_{23}H_{18}N_4O_3$	398.41	96°C	75	0.36
QO-10		$C_{25}H_{23}N_5O$	425.48	91°C	61	0.47

Table 3. FT-IR Spectral data of the compounds

Compound	FT-IR (KBr υ cm^{-1})
Q-1(Step 1)	3308 (N-H str), 1653 (C=O, carboxamide), 1609 (C-N)
Q-2(Step 2)	1653 (C=O), 1609 (C=N), 1291 (C-O ether), 2851(CH aliphatic)
Q-3(Step 3)	3304- 2922 (NH, NH_2), 2848 (C-H aliphatic), 1653 (CO, Carboxamide), 1615 (C=N), 1300 (C-O-C)
QS-7	3394 (NH str.), 3022 (Aromatic CH str.), 1653 (C=O str.), 1617 (C=N str.), 1252 (Asymmetric C-O-C str.), 1026 (Symmetric C-O-C str.),
QO-7	3320 (NH str.), 2960 (Aromatic CH str.), 1302 (Asymmetric C-O-C str.), 1097 (Symmetric C-O-C str.), 1158 (C-O-C ring str.).
QS-6	3308 (NH str.), 3046 (Ar-CH str.), 1654 (C=O str.), 1615(C=N str.), 860 (aliphatic CH stretching of N=CH), 1300 (C-O-C ether), 1257 (C-N str.), 1485 (Ar C-C str.), 1511 (N=O, asymmetric), 1363 (N=O, symmetric)
QO-6	3385 (Aromatic CH str.), 1531 (Ar NO_2, N=O str. asymmetric), 1302 (N=O srt. symmetric), 1674 (C=N str.), 1158(C-O-C ring str.), 817(CN str. Ar NO_2), 1455(CN str. ring)
QO-5	3423 (Aromatic CH str.), 1526 (Ar NO_2, N=O str. asymmetric),1342 (N=O, symmetric), 1158(C-O-C ring str.), 817 (CN str. Ar NO_2),
QO-4	1528 (C=C aromatic str.), 3463 (OH phenolic str.), 3428 (NH str.), 1305 (OH bending), 1677 (C=N str.), 1158 (C-O-C ring asymmetric str.), 1097 (C-O-C ring symmetric str.)

Table 4. ^{1}HNMR Spectral Analysis of QO-4

Compound	^{1}HNMR
QO-4	OH (s, 5.0), CH_2 (s, 4.79), NH (s, 4.0), CH- methine (s, 5.55), Aromatic protons (m, 6.61-7.31)

Table 5. Mass Spectral Analysis of QO-4

Compound	Molecular ion peak (m/z)	Base peak (m/z)
QO-4	398.40	237.1

Table 6. Anticancer activity of selected Oxadiazole-quinazoline analogues On HCT 116 (Human colon) cancer cell lines

Compound	Percentage viability (%) Concentration (µg/ml)		
	10 µg/ml	20 µg/ml	30 µg/ml
5-fluorouracil (std)	56.5	51.4	47.3
QO-1	85.4	79.1	74.5
QO-4	71.3	68.6	61.6
QO-5	78.1	73.7	70.6
QO-6	80.9	76.2	73.2

Figure 1: MTT assay of selected oxadiazole-quinazoline analogues on HCT 116

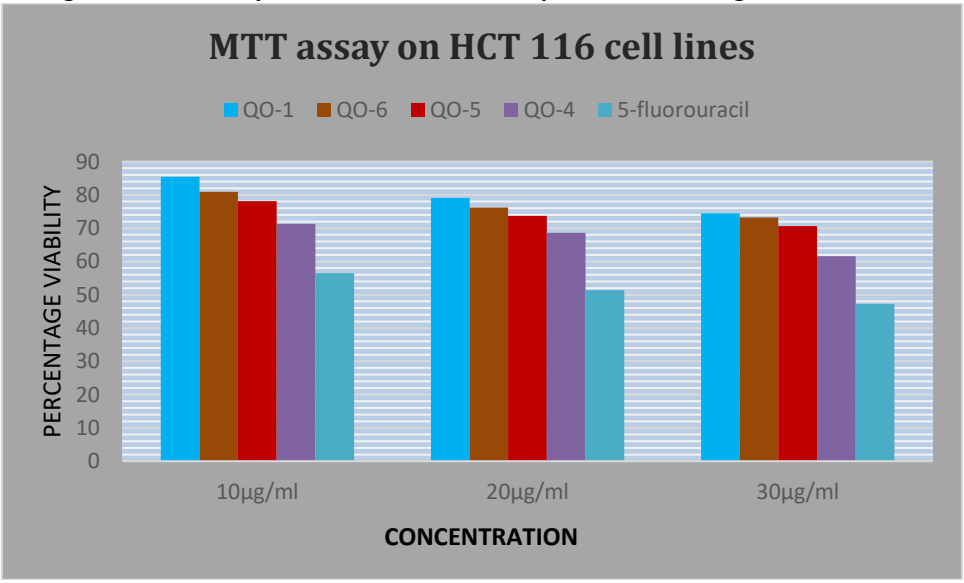
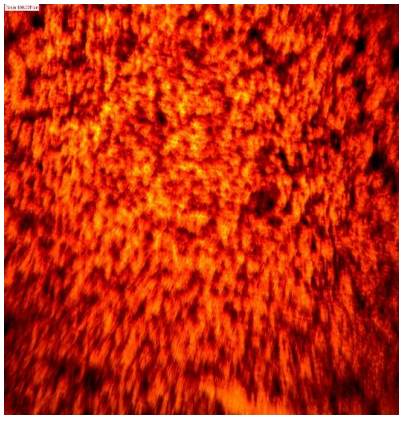
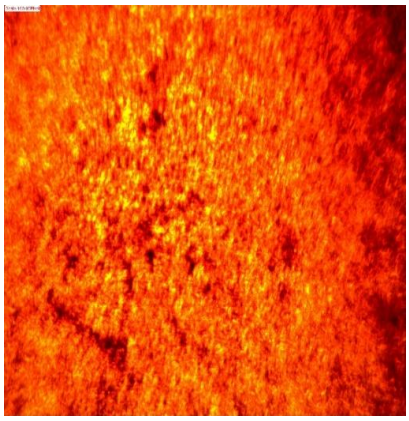


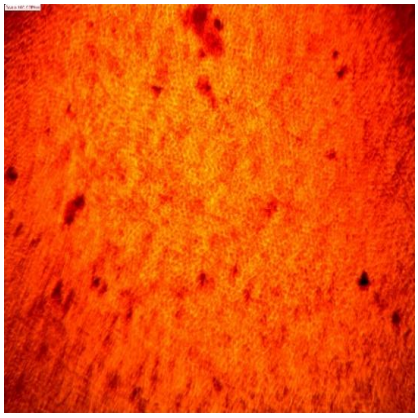
Figure 2: Images of compounds for MTT assay on HCT 116



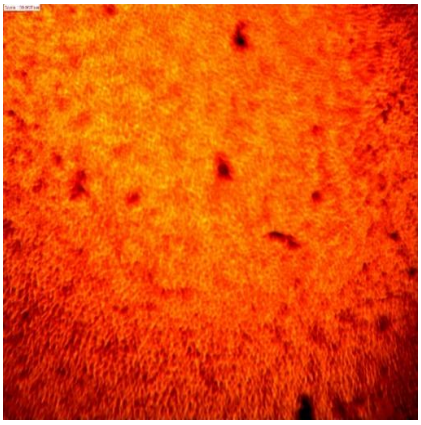
Control



QO-4 (10µg/ml)

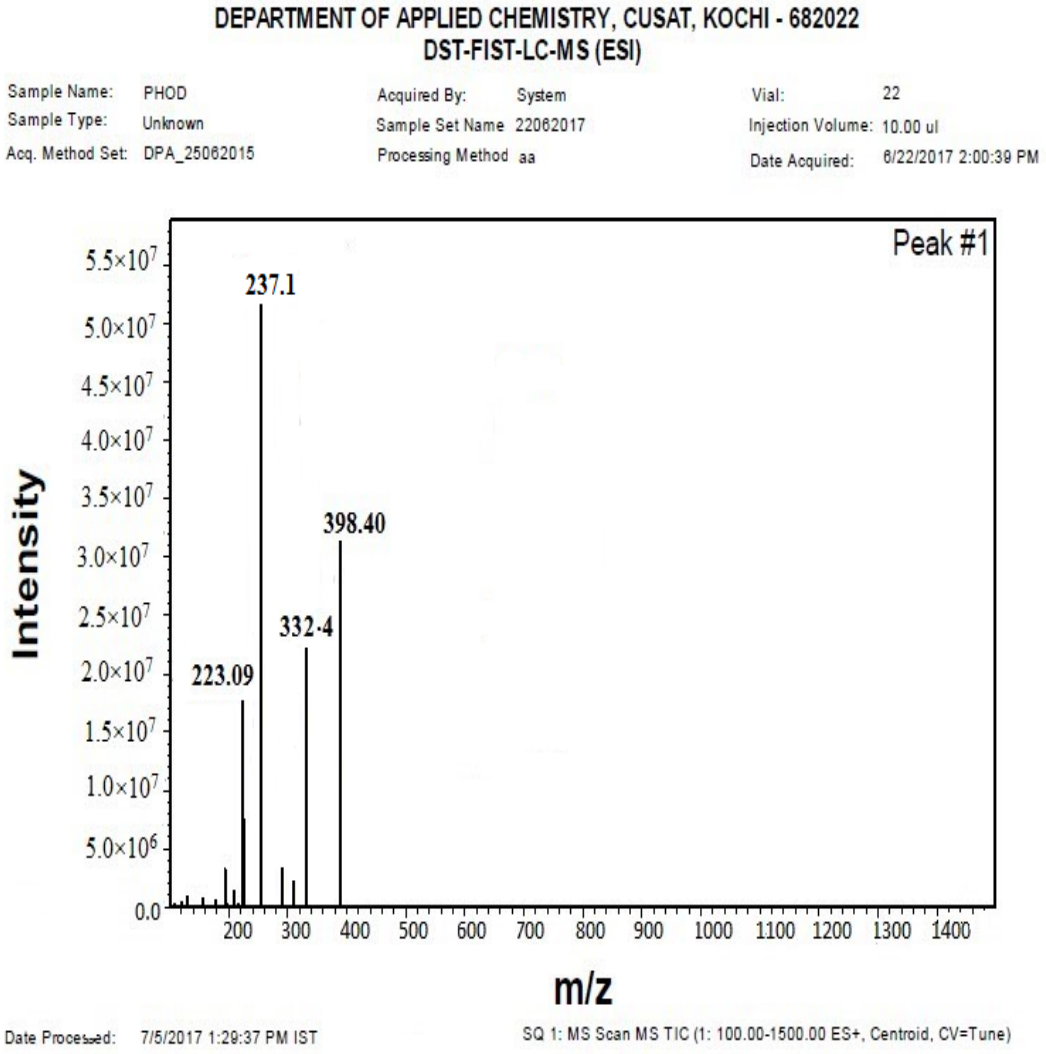


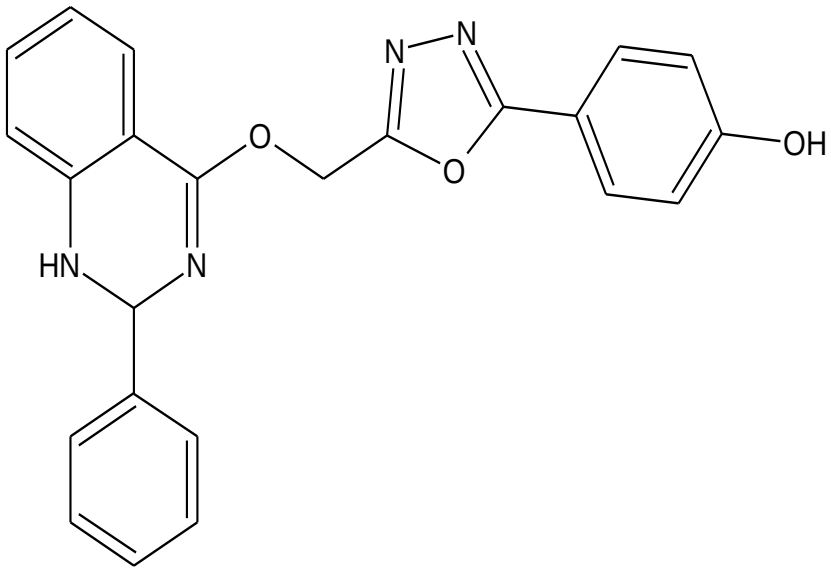
QO-4 (20µg/ml)



QO-4 (30µg/ml)

Figure 3. Mass spectra of compound QO-4





c\21ccccc1NC(/N=C/2OCc3nnc(o3)c4ccc(cc4)O)c5ccccc5

4-(5-{[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)phenol

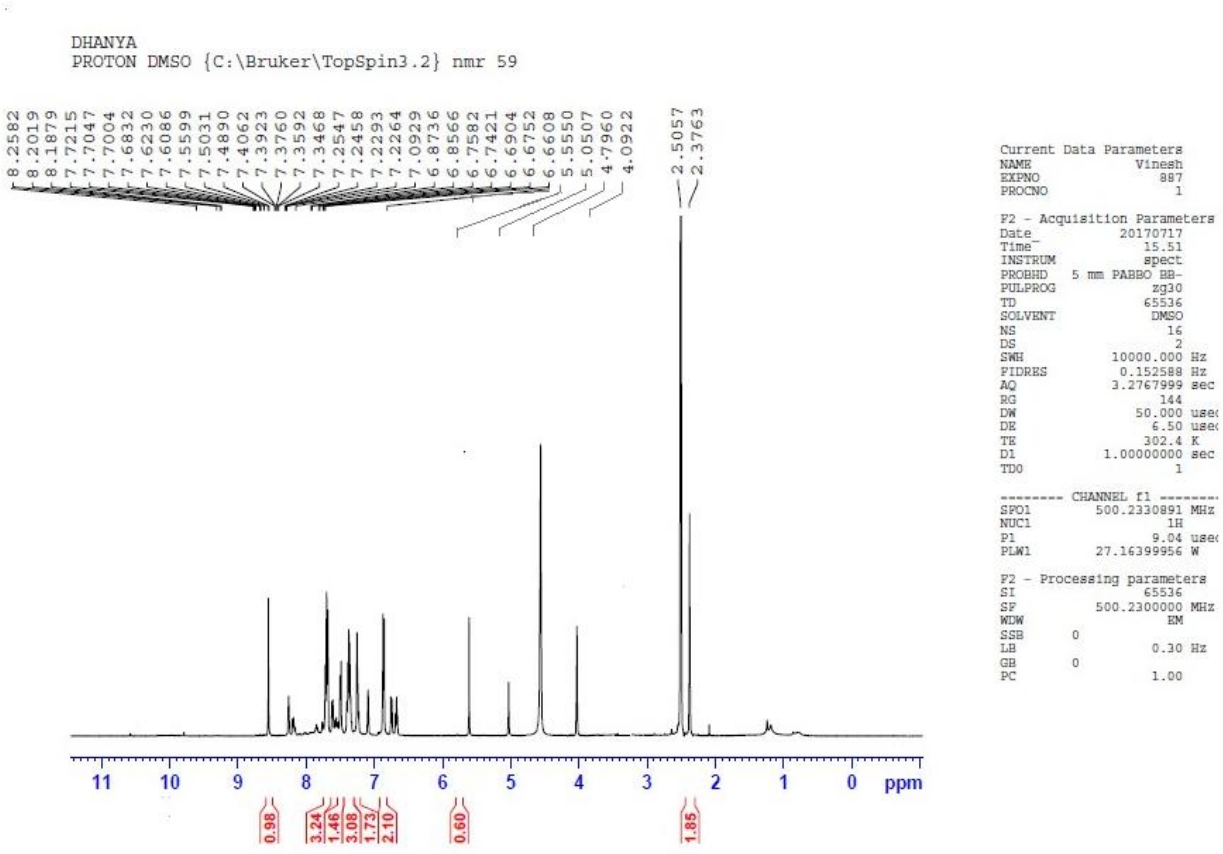
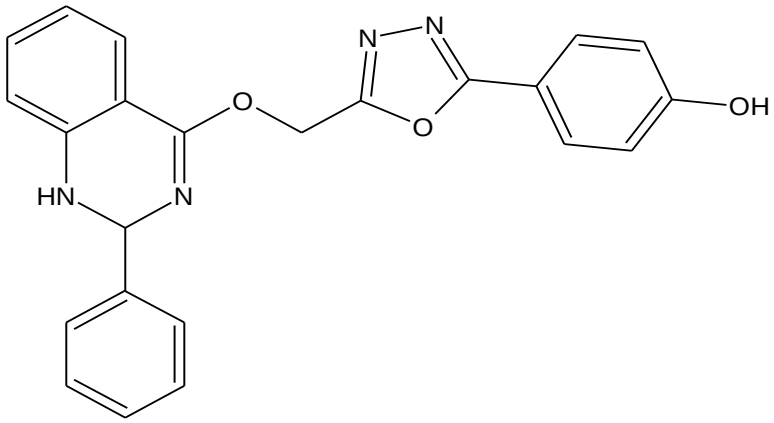


Figure 4. ^{1}H NMR SPECTRA OF COMPOUND QO-4



c\21ccccc1NC(/N=C/2OCc3nnc(o3)c4ccc(cc4)O)c5ccccc5

4-(5-{[(2-phenyl-1,2-dihydroquinazolin-4-yl)oxy]methyl}-1,3,4-oxadiazol-2-yl)phenol

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