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Design, Synthesis, Molecular Docking, *In-vitro* Anticancer and Antibacterial Evaluation of Novel Pyrazole Linked with Quinazoline Scaffolds

MOHD. AFROZ[1]* and G. SHIVA KUMAR[2]

*[1]Department of Pharmaceutical Chemistry, GITAM School of Pharmacy, GITAM (Deemed to be University), Sangareddy-502329, India.
[2]GITAM School of Pharmacy, GITAM (Deemed to be University), Sangareddy-502329, India.
*Corresponding author E-mail: mohdafroz1992@gmail.com, sgubbiya@gitam.edu

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ABSTRACT

A novel series of compounds are synthesized N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxo-3-(3,5-diphenyl-2H-pyrazol-1(5 H)-yl) propenamide (3a-l). All the synthesized compounds are characterized by different spectral tools ^{1}HNMR, IR, ^{13}CNMR, and MASS. It was screened as *in vitro* anticancer and antibacterial activity. Among the synthesized compounds 3d and 3e exhibit potent against three cancer cell-line MCF7, PC-3, HT-29. IC_{50}(µM) 3d (16.52, 13.24, 10.15 µg/mL) 3e (17.28, 15.26, 12.33 µg/mL) with standard drugs doxorubicin (15.29, 12.26, 9.06 µg/mL) and 5-fluorouracil (16.15, 13.73, 10.25 µg/mL). Antibacterial activity 3d, 3e, 3j, 3k scaffolds exhibit a promising activity with the standard drug ciprofloxacin. Insilico molecular docking is examined, Its predicted a good binding affinity against with 5C5S, 6XXN, 3K46 proteins.

Keywords: Pyrazole, Quinazoline, Anti-cancer, Anti-bacterial, Molecular docking.

INTRODUCTION

One of the most common aberrant cell growths in the human body is cancer. Death rates from cancer exist. If cancer is detected in its early stages, it can be cured; if it is detected in its later stages, there are few possibilities that it can be cured.[1]

Heterocyclic chemistry becomes more challenging for medicinal chemists. Heterocyclic compounds and their derivatives show various pharmacological and clinically active. Heterocyclic molecules have diversified action in various pharmacological and therapeutic activities.[2] The organic molecules are distributed in nature and play an essential role in regulating biological processes. Fused heterocyclic moieties like pyrazole and quinazoline nucleus are significant in the drug discovery process The heterocyclic compounds like pyrazole,[3] quinazoline[4] nucleus contain prominent electron withdrawing groups like nitrogen and oxygen atom. They have the potency to bind the receptor and show an agonist effect to receptor and it exhibit molecular inhibitory binding

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with biological systems. Due to their privilege and efficacy towards pharmacological significance. It has wide-linked properties of Pyrazole and quinazoline nucleus has a key role of inhibiting certain receptors like aurora kinase inhibitors 5 cyclin-dependent kinases (CDK) inhibitors,[5] reticular activating system-neuroendocrine tumor (Ras-Net),[5] DNA binding agent,[5] epithelial growth factor receptor (EPGR)[6] inhibitor, cyclo-oxygenase(COX),[7] lipoxygenase(LOX)[7] inhibitors and tubulin inhibition polymerization[8] further active inhibitory receptor is represented in Fig. 1[9] It attach to different hetero molecules scaffolds published in the literature data for the potency compounds has with a wide range of therapeutic properties. Pyrazole[10] and quinazoline[11] core moiety exhibit diverse pharmacological and therapeutic properties such as anticancer,[12] anti-mycobacterial,[13] antidiabetic,[14] anti-inflammatory,[15] antimicrobial,[16] anti-leishmanial,[17] anti-hypertensive agents α-blocking,[18] Neuroprotective agents[18] as approved by USFDA drugs are shown in Figure2

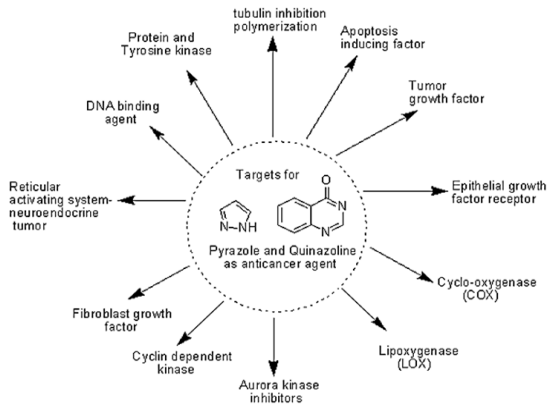

Fig. 1. Importance of inhibitory activity of Pyrazole and Quinazoline nucleus

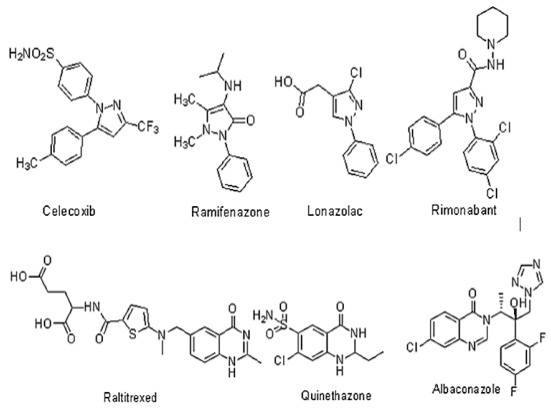

Fig. 2. USFDA-approved drugs Pyrazole and Quinazoline nucleus

Extremely efforts to develop a synthesis of pyrazole linked with quinazoline and its scaffolds. In our research, grateful to these pyrazole and quinazoline hybrids in continuation of our work towards biologically active molecules.[19] In this research our aim to synthesized newly novel pyrazole and quinazoline hybrids via Schiff mechanisms and mannish base mechanism and its scaffolds (3a-l). Synthesized scaffolds are promising against cancer cell lines MCF-7, PC-3, and HT-29 by using MTT assay methods. Antibacterial activity is screened by using the agar-diffusion method and insilico molecular docking[20] is performed.

MATERIALS AND METHODS

All the chemicals were purchased from SD Fine and AURA Laboratories Analytical research grades. Then further characterization by different analytical techniques like silica gel (TLC) Thin layer chromatography and IR spectroscopy (BRUKER), ^{1}H-NMR spectroscopy (400 MHz AvanceCore), ^{13}C spectroscopy (Avance 400 MHz), Mass spectrometry (Thermo fisher scientific Orbitrap Exploris 120) and Melting point (LB-MPS8). Anti-cancer activity were performed by using MTT assay and antibacterial activity were performed by using bacterial strain and in silico molecular docking are predicted.

Synthesis of N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxo-3-(3,5-diphenyl-2H-pyrazol-1(5 H)-yl) propanamide.

The procedure consist of three steps.

Step I: Synthesis of Chalcones

Acetophenone and different substituted benzaldehydes an add ethanol Stirr at magnetic stirrer at room temperature 1 h by using Claisen-Schmidt condensation mechanism and the reaction was observed in TLC. The reaction crude product was filter and recrystallized with ethanol and finally obtained a chalcone moiety.

Step II: Synthesis of Quinazoline malonic dihydrazide

Take Malonic di-hydrazide and add 2-methyl benzoxazine-4-one and add pyridine and refluxed for 3 hours. In reaction mixture add crush ice or cold water neutralised with dil HCl. Filter the crude product and Precipitate were collected, dry the obtained product and it was recrystallized with methanol or ethanol.

Step III: Synthesis of Pyrazole Scaffolds (3a-3l)

Chalcone of step1 and malonic-dihydrozido quinazoline step2 was taken in RBF and add glacial acetic acid and add NaOH (40% 10 mL) then reflux for 5 hours. The reaction undergo cyclization schiff and mannish base mechanism formation of pyrazole and its scaffold (3a-l). The progress of the reaction mixture was monitored in TLC cooled with rinse water and add crushed ice. Filter the reaction and obtain solid residue, dry the residue, and recrystallized with ethanol.

Biological activity evaluation

***In-vitro* Anti-cancer activity**

Anti-cancer activity were evaluated (3a-l) against three cancer cell line breast cancer (MCF7) and prostate cancer (PC-3) and human colon cancer (HT-29) by using MTT assay method[21], Trypsinization of the cells and trypan blue assay were performed to determine the viability of the cells in suspension. Trypsinization of the cells and trypan blue assay were performed to determine the viability of the cells in suspension. The cells were then counted using a hemocytometer (IMPROVED B.S.748 NEUBAUER by Rohem india, and a density of $5.0X10^3$ cells per well were seeded 100µL in culture medium in 96 well plates, and incubated Manufacturer Thermo scientific Model Co2 incubator model 370 manual for 12 h at 37^0C. Removed the existing medium, then filled each well with new media. Following that, plates were incubated for three hours at 37^0C. Precipitations were produced at the end of the incubation time as a result of the MTT salt being reduced to chromophore-Formosan crystals by cells with metabolically active mitochondria. The optical density of crystals that had been dissolved in DMSO was calculated at 570nm on a microplate reader using a FlexStation3 plate reader. The standard formula for calculating cell toxicity is (average OD*100/positive control)-100, and figures for the concentration of the test drug needed to hinder cell development by 50% (IC_{50}) were utilized.

***In-vitro* Antibacterial activity**

Antibacterial activity was evaluated (3a-l) against *Gram-positive* and *Gram-negative* bacterial strains by using agar plate diffusion method.[22] It is examined that the view a dose-dependent inhibition of bacterial growth.

Insilico Molecular docking studies

The insilico molecular docking studies were predicted in Autodock vina PyRx 0.8.23 This tool was analyze and predict the ligand and completely bound to the receptor. Viewed in 3D structure. The protein was downloaded from WWW.RCSBPDB.COM (23) PDB: 5C5S (Human-myosin9b Rhogap), 6XXN (sting CTD complex), 3K46 (*E.coli* beta glucurinadase) and finally docking visualization analysis was predicted in Discovery Studio and Molegro Molecular Viewer.

Spectral data of newly synthesized compound

3a: N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxo-3-(3,5-diphenyl-2H-pyrazol-1(5H)-yl) propanamide.IR: 3413(-NH), 3377(-NH), 3134 (-CH), 2989(-CH_3), 2892(-CH), 1725 (C=O), 1700 (C=O), 1555(C=N), 1295(C-N). ^{1}H NMR: 12.1 (1H, -NH), 11.33(1H, -NH), 8.4- 6.9(13H Ar), 6.35 (1H, -CH), 3.2 (1H, -CH_2), 2.42(3H, -CH_3). ^{13}C NMR 127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4 MASS (ESI) m/z: 466 $[M+H]^+$

3b: N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxo-3-(5-phenyl-3-p-tolyl-2H-pyrazol-1(5 H)-yl) propanamide. IR: 3455 (-NH), 3302(-NH), 3102(-CH), 2957(-CH),1700 (C=O), 1670 (C=O), 1585(C=N), 1252(C-N). ^{1}H NMR: 12.5 (1H, -NH,),11.3(1H, -NH), 8.0- 6.9(13H Ar), 6.83 (1H, -CH), 3.42 (1H, -CH_2), 2.34 (3H, -CH_3). 1.90 (3H, -CH_3). ^{13}C NMR 127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4, 19.9, 24.3 MASS (ESI) m/z: 478 $[M+H]^+$

3c: 3-(3-(4-methoxyphenyl)-5-phenyl-2H-pyrazol-1(5 H)-yl-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxopropanamide. IR: 3395 (-NH), 3355(-NH), 3144(-CH), 2980(-CH_3), 2895(-CH), 1715 (C=O), 1710 (C=O), 1545(C=N), 1285(C-N), 1245(C-O-C-OCH_3). ^{1}H NMR: 11.9 (1H, -NH), 10.3 (1H, -NH), 8.0- 6.9 (13H Ar), 6.55 (1H, -CH), 3.4 (1H, -CH_2), 2.4 (3H, -CH_3). 2.33 (3H, -OCH_3). ^{13}C NMR 127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4, 159.9, 55.9 MASS (ESI) m/z: 496 $[M+H]^+$.

3d: N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-(3-(4-nitrophenyl)-5-phenyl-2 H-pyrazol-1(5 H)-yl)-3-oxopropanamide. IR: 3395 (-NH), 3365 (-NH),

3133(-CH), 2945(-CH_3), 2900 (-CH),1710 (C=O), 1715 (C=O), 1590 (-NO_2), 1550 (C=N), 1290 (C-N), ^{1}H NMR: 12.0 (1H, -NH), 11.3 (1H, -NH), 8.0- 6.9 (13H Ar), 6.7 (1H, -CH), 3.0 (1H, -CH_2), 2.10 (3H, -CH_3) ^{13}C NMR 127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4, 127.3, 121.0 MASS (ESI) m/z: 511 $[M+H]^+$.

3e: 3-(3-(4-chlorophenyl)-5-phenyl-2H – pyrazol-1(5 H)-yl-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxopropanamide IR: 3415 (-NH), 3385 (-NH), 3145 (-CH), 2960(-CH_3),2890 (-CH),1710 (C=O), 1695 (C=O), 1570 (C=N), 1265 (C-N), 890 (C-Cl). ^{1}H NMR: 12.0 (1H, -NH), 11.2 (1H, -NH), 8.0- 6.8(13H), 6.25(1H, -CH), 3.2 (1H, -CH_2), 2.2 (3H, -CH_3) ^{13}C NMR 127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4, 133.5, 128.8, 127.8 MASS (ESI) m/z: 500 $[M+H]^+$.

3f: 3-(3-(3,4-dimethoxyphenyl)-5-phenyl-2H – pyrazol-1(5 H)-yl-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxopropanamide IR: 3403 (-NH), 3333(-NH), 3160 (-CH), 2955 (-CH_3), 2890 (-CH), 1710 (C=O), 1705 (C=O), 1535 (C=N), 1295 (C-N), 1255 (C-O-C-OCH_3). ^{1}H NMR: 12.2 (1H, -NH), 11.4 (1H, -NH), 8.00- 6.8 H), 6.2 (1H, -CH), 3.05 (1H, -CH_2), 2.0(3H, -CH_3). 2.0 (6H, -OCH_3) ^{13}C NMR 127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4, 111.6, 128.8, 127.8 MASS (ESI) m/z: 526 $[M+H]^+$.

3g: N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxo-3-(3-phenyl-5-p-tolyl-2H-pyrazol-1(5 H)-yl) propanamide. IR: 3380 (-NH), 3345 (-NH), 3125 (-CH), 2975(-CH_3), 2855 (-CH),1690 (C=O), 1700 (C=O), 1535 (C=N), 1240 (C-N). ^{1}H NMR: 11.2 (1H, -NH), 10.3 (1H, -NH), 8.0- 6.8 (13H Ar), 6.5 (1H, -CH), 3.6 (1H, -CH_2), 2.45 (3H, -CH_3), 1.7 (3H, -CH_3) ^{13}C NMR 127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4, 24.3, 126.4, 128.7 MASS (ESI) m/z: 478 $[M+H]^+$.

3h: N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxo-3-(3,5-di p-tolyl-2H-pyrazol-1(5 H)-yl) propanamide. IR: 3385 (-NH), 3340 (-NH), 3105 (-CH), 2955 (-CH_3), 2875 (-CH),1720 (C=O), 1715 (C=O), 1565 (C=N), 1235 (C-N). ^{1}H NMR: 12.3 (1H, -NH), 11.4 (1H, -NH), 8.0- 6.8 (13H, Ar), 6.3 (1H, -CH), 3.0 (1H, -CH_2), 2.05(3H, -CH_3), 1.9 (6H, -CH_3) ^{13}C NMR 127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4, 126.3, 24.3, 24.3 Mass (ESI) m/z: 494 $[M+H]^+$.

3i: 3-(3-(3,4-methoxyphenyl)-5-p-tolyl-2H-pyrazol-1(5 H)-yl-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxopropanamide IR: 3425 (-NH), 3390 (-NH), 3145 (-CH), 2930 (-CH_3), 2880 (-CH),1720 (C=O), 1700 (C=O), 1570 (C=N), 1295 (C-N), 1235 (C-O-C-OCH_3). ^{1}H NMR: 12.0 (1H, -NH), 11.1 (1H, -NH), 8.0- 6.7 (13H, Ar), 6.0 (1H, -CH), 3.0 (1H, -CH_2), 2.40 (3H, -CH_3), 2.0 (3H, -OCH_3), 1.85 (3H, -CH_3) ^{13}C NMR 127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4, 127.4, 24.3, 55.9 Mass (ESI) m/z: 510 $[M+H]^+$.

3j: N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-(3-(4-nitrophenyl)-5- p-tolyl-2H-pyrazol-1(5 H)-yl) -3-oxopropanamide IR: 3370 (-NH), 3337(-NH), 3140 (-CH), 2920 (-CH3), 2885 (-CH),1710 (C=O Str), 1700 (C=O), 1580(-NO_2), 1555 (C=N), 1280 (C-N). ^{1}H NMR: 12.0 (1H, -NH), 11.2 (1H, -NH), 8.1- 6.8 (13H, Ar), 6.5 (1H, -CH), 3.5 (1H, -CH_2), 2.5 (3H, -CH_3), 1.5 (3H, -CH_3) ^{13}C NMR 127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4, 121, 127.3, 24.3 MASS (ESI) m/z: 530 $[M+H]^+$.

3k:3-(3-(4-chlorophenyl)-5-p-tolyl-2H-pyrazol-1 (5 H)-yl-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxopropanamide IR: 3375 (-NH), 3330 (-NH), 3110 (-CH), 2935 (-CH_3), 2836 (-CH), 1700 (C=O), 1690 (C=O), 1555 (C=N), 1290 (C-N), 878 (C-Cl). ^{1}H NMR 6.3 (1H, -CH), 3.1 (1H, -CH_2), 2.5 (3H, -CH_3), 1.9 (3H, -CH_3) ^{13}C NMR 127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4, 128.8, 127.8, 24.3 MASS (ESI) m/z: 514 $[M+H]^+$.

3l: 3-(3-(3,4-dimethoxyphenyl)-5-p-tolyl-2H-pyrazol-1(5 H)-yl-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxopropanamide IR: 3385(NH) 3360 (NH) 3115 (CH) 2925 (CH_3) 2889 (CH) 1700 (C=O), 1690 (C=O), 1555 (C=N), 1290 (C-N), 1225 (OCH_3). ^{1}H-NMR: 12.2 (1H, -NH), 11.3 (1H, -NH), 8.2-6.8 9 (13H, Ar), 6.15(1H, -CH) 3.3 (1H, -CH_2),2.5 (6H, -OCH_3), 2.7 (3H, -CH_3), 1.8 (3H, -CH_3) ^{13}C NMR

127.4, 133.5, 12.4, 147.1, 120.9, 128.8, 164, 161, 19.9, 170.3, 44.5, 95.3, 61, 134, 128.7, 128.0, 128.7, 126.4, 24.3, 56.2, 56.2 MASS (ESI) m/z: 540 $[M+H]^+$.

RESULTS AND DISCUSSION

Chemistry

The research is focused on the precise synthesis of novel N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxo-3-(3,5-diphenyl-2H-pyrazol-1 (5 H)-yl) propanamide (3a-l). The step1 is synthesized chalcones by using Claisen-Schmidt condensation and step2 are synthesized Quinazoline malonic dihydrazide step3 undergoes cyclization Schiff and Mannish base mechanism formation of pyrazole and its scaffold (3a-l) and are confirmed by using different spectral analysis tools ^{1}HNMR, ^{13}CNMR, IR and Mass. The completed scheme is represented in Fig. 3 and the Physical properties are shown in Table 1.

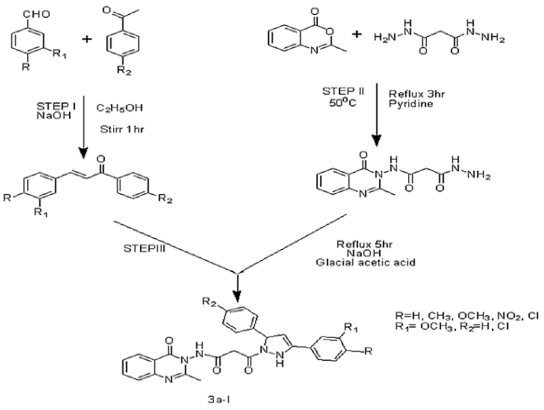

Fig. 3. Scheme I of novel pyrazole linked with quinazoline scaffolds (3a-3l)

Table 1: Physical properties of novel pyrazole linked with quinazoline scaffolds (3a-3l)

Compounds	Molecular formula	Molecular weight	R	R_1	R_2	Melting point	Yield %
3a	$C_{27}H_{23}N_5O_3$	465.15	H	H	H	246°C	78%
3b	$C_{28}H_{25}N_5O_3$	479.12	CH_3	H	H	287°C	88%
3c	$C_{28}H_{25}N_5O_4$	495.08	OCH_3	H	H	324°C	86%
3d	$C_{27}H_{22}N_6O_5$	510.07	NO_2	H	H	276°C	78%
3e	$C_{27}H_{22}N_6O_3Cl$	499.9	Cl	H	H	245°C	84%
3f	$C_{29}H_{27}N_5O_5$	525.16	OCH_3	OCH_3	H	345°C	72%
3g	$C_{28}H_{25}N_5O_3$	479.11	H	H	CH_3	226°C	85%
3h	$C_{29}H_{27}N_5O_3$	493.02	CH_3	H	CH_3	245°C	78%
3i	$C_{29}H_{27}N_5O_4$	509.02	OCH_3	H	CH_3	280°C	90%
3j	$C_{28}H_{24}N_6O_5$	529.01	NO_2	H	CH_3	252°C	89%
3k	$C_{28}H_{24}N_5O_3Cl$	513.18	Cl	H	CH_3	245°C	78%
3l	$C_{30}H_{29}N_5O_5$	539.13	OCH_3	OCH_3	CH_3	315°C	82%

Biological Activity

In-vitro Anticancer Activity

In our research. A Novel series of compounds are synthesized and evaluated as *in-vitro* anticancer activity (3a-l) were assessed against three cell lines (MCF7) and (PC-3) and (HT-29) by using MTT assay method 3d and 3e were found potent against all the three cell lines IC_{50}(μM) 3d (16.52,13.24.10.15 μg/mL) 3e (17.28, 15.26, 12.33 μg/mL) compared with standard drug Doxorubicin (15.29, 12.26, 9.06 μg/mL) and 5-Fluorouracil (16.15, 13.73, 10.25 μg/mL). The IC_{50} values are represented in Table 2 and the standard graph is represented in Figure 4.

In-vitro Antibacterial activity

In our research *in vitro* Antibacterial activity was screened. The novel series of compounds are synthesized (3a-l) was examined against two *Gram-positive* and two *Gram-negative* bacteria strains by using the agar plate method. Interestingly, (3d, 3e, 3j, 3k) were potent and active against both the bacterial strains. The percentage zone of inhibition values are represented in Table 3 The results show that the substituted of 3d Nitrogen, 3e Chlorine, 3j Methyl and Nitrogen, 3k Methyl and Chlorine substituted compound shows a promising activity comparison with ciprofloxacin.

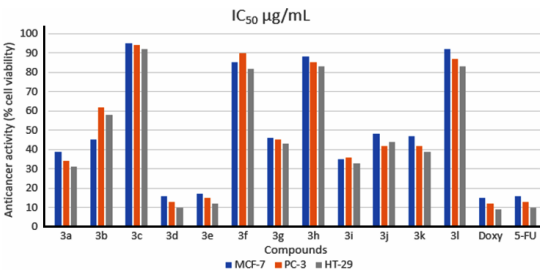

Fig. 4. Graphical representation of Anticancer activity of novel pyrazole linked with quinazoline scaffolds

Table 2: Anticancer activity of novel pyrazole linked with quinazoline scaffolds IC_{50} values (3a-3l)

Compounds	IC_{50} (μM) MCF-7	PC-3	HT-29
3a	39.26 ± 0.32	34.32 ± 0.41	31.26 ± 0.49
3b	45.59 ± 0.51	62.18 ± 0.25	58.15 ± 0.16
3c	95.23 ± 0.86	94.16 ± 0.48	92.23 ± 0.27
3d	16.52 ± 0.052	13.24 ± 0.044	10.15 ± 0.032
3e	17.28 ± 0.065	15.26 ± 0.072	12.33 ± 0.068
3f	85.19 ± 0.16	90.69 ± 0.58	82.22 ± 0.32
3g	46.02 ± 0.27	45.34 ± 0.32	43.26 ± 0.62
3h	88.21 ± 0.48	85.26 ± 0.51	83.45 ± 0.38
3i	35.12 ± 0.21	36.44 ± 0.64	33.19 ± 0.55
3j	48.14 ± 0.71	42.14 ± 0.16	44.28 ± 0.67
3k	47.25 ± 0.25	42.19 ± 0.56	39.15 ± 0.42
3l	92.45 ± 0.68	87.21 ± 0.69	83.24 ± 0.22
DOXORUBICIN	15.29 ± 0.032	12.26 ± 0.041	9.06 ± 0.028
5-FLUROURACIL	16.15 ± 0.016	13.73 ± 0.025	10.25 ± 0.018

Table 3: Antibacterial activty of novel pyrazole linked with quinazoline scaffolds (3a-3l)

	Gram-positive bacteria				*Gram-negative bacteria*			
	Staphylococcus aureus		*Bacillus subtilis*		*Escherichia coli*		*Pseudomonas aeruginosa*	
Compounds	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 g/mL	100 μg/mL	50 μg/mL	100 μg/mL
3a	20	23	8	19	18	21	20	14
3b	14	17	11	13	10	12	12	16
3c	11	17	9	12	13	14	15	18
3d	25	30	24	27	24	28	27	30
3e	25	31	23	27	25	29	27	31
3f	7	10	10	13	15	18	17	20
3g	12	15	15	17	10	12	14	19
3h	11	14	10	12	15	11	8	18
3i	9	10	12	8	13	8	12	10
3j	22	27	18	20	21	22	19	25
3k	23	29	19	21	23	26	22	27
3l	14	15	10	13	9	12	11	14
Ciprofloxacin	28	33	25	29	27	32	30	34

Insilico Molecular docking

The insilico molecular docking was analyzed by using Autodock vina PyRx (0.8). The Autodock vina tool shows the accurate result, whenever software is run for trail the docking and binding affinity values are standard and accurate. The protein was downloaded from WWW.RCSBPDB. COM The protein and ligands are uploaded in PyRx tool and adjust coordinates of the x and y-axis. Then, This tool detects interaction with different amino acids and binding affinity values have been predicted in Excel file. Finally obtained binding affinity values and 2D and 3D images. It can be viewed by using tools like Discovery Studio and Molegro Molecular Viewer. The binding affinity values are represented in Table 4 and interaction with different amino acids is represented in Figure 5 and 6.

Table 4: *In-silco* molecular docking binding affinity values of novel pyrazole linked with quinazoline scaffolds (3a-3l)

Compounds	Binding-Affinity Kcal/mol 5C5S	6XXN	3K46
3a	-10.3	-10.3	-11.2
3b	-10.9	-10.7	-10.2
3c	-10.5	-10.2	-10.5
3d	-13.5	-12.8	-13.3
3e	-12.8	-11.9	-12.6
3f	-9.5	-10.8	-10.6
3g	-10.9	-10.6	-11.4
3h	-11.3	-10.8	-11.7
3i	-10.9	-10.4	-10.7
3j	-11.2	-10.8	-12.2
3k	-11.1	-11.0	-11.8
3l	-11.0	-10.1	-10

In our research. Insilico Molecular docking was performed and obtained good binding affinity values against PDB ID 5C5S (human myosin 9b RhoGAP), 6XXN (sting CTD complex), 3K46 (*E. coli* beta glucurinadase). The binding affinity of the ligand 3d and 3e against proteins is around-12 kcal/mol. The ligand coupled with various amino acids Thr112(A), Gln108(A), Asn139(A), Tyr111(A), Gly110(A), Ala391(A) and Ile143(A). The molecules binds to protein through its 2D and 3D complex. The protein and ligand bind and coupled with different amino acid interactions are completely moulded each other. In figure the ligand and protein mould through its 3D complex.

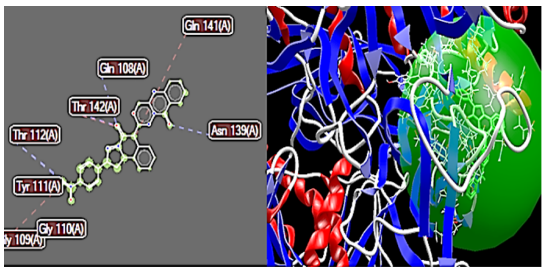

Fig. 5. Interaction image of 3d with human myosin 9b RhoGAP (Pdb id–5C5S)

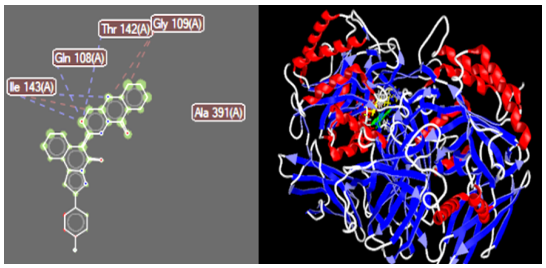

Fig. 6. Interaction image of 3e with *E. coli* beta glucurinadase (Pdb id–3k46)

CONCLUSION

In this research, The Novel series of compounds are synthesized N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxo-3-(3,5-diphenyl-2H-pyrazol-1(5H)-yl) propanamide (3a-l). The synthesized derivatives are characterized by ^{1}HNMR, ^{13}CNMR, IR, and MASS. It was evaluated as invitro anticancer and antibacterial activity. Among the series of compounds 3d and 3e exhibit potent against three cancer cell lines MCF7, PC-3, HT-29. IC_{50}(μM) 3d (16.52, 13.24, 10.15 μg/mL) 3e (17.28, 15.26, 12.33 μg/mL) with standard drugs doxorubicin (15.29, 12.26, 9.06 μg/mL) and 5-fluorouracil (16.15, 13.73, 10.25 μg/mL). And also screened antibacterial activity by using agar plate diffusion methods 3d, 3e, 3j, 3k scaffolds exhibit a promising activity compared with the standard drug ciprofloxacin. In our research interestingly withdrawing group attached with scaffolds it shows a more active anti-cancer activity as well as antibacterial activity and also shows based on withdrawing capability. Insilico Molecular Docking performed and it is predicted a good binding affinity against 5C5S (Human-myosin9b-Rhogap), 6XXN (sting CTD complex), 3K46 (*E. coli* beta glucurinadase) proteins.

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Conflicts of Interest

There are no conflicts of interest declared by the authors.

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