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ORIGINAL ARTICLE **OPEN ACCESS**

Synthesis and Biological evaluation of Novel Quinazoline derivatives as Anticancer, Antibacterial and Antifungal agents

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ABSTRACT
Some novel 4-(substituted aniline)quinazoline were synthesized in good yields and evaluated for their possible antibacterial, anti-fungal and anticancer activities and acute toxicity. The structures of the synthesized compounds were confirmed on the basis of their spectral data and elemental analysis. Their antibacterial activity evaluated by the agar cup method while their anti-fungal activities were evaluated by poison plate method and in-vitro anticancer activity by using HeLa & MCF-7 cell line. Quinazoline derivatives had failed to produce antibacterial activity against the gram negative strains but possess the weak antibacterial activity against the gram positive strains. In other hand, the substitution, 4-bromo and 3-nitro in compound 2(S2), on 4-aniloquinazoline ring had shown the strong antifungal activity (90%) against Fusarium moniliforme, hence it is equipotent with Griseofulvin. These compound suggesting that it could be useful in the treatment of fungal infection.
Keywords: *Antibacterial Activity, Anticancer Activity, Antifungal Activity, Quinazoline, Synthesis.*

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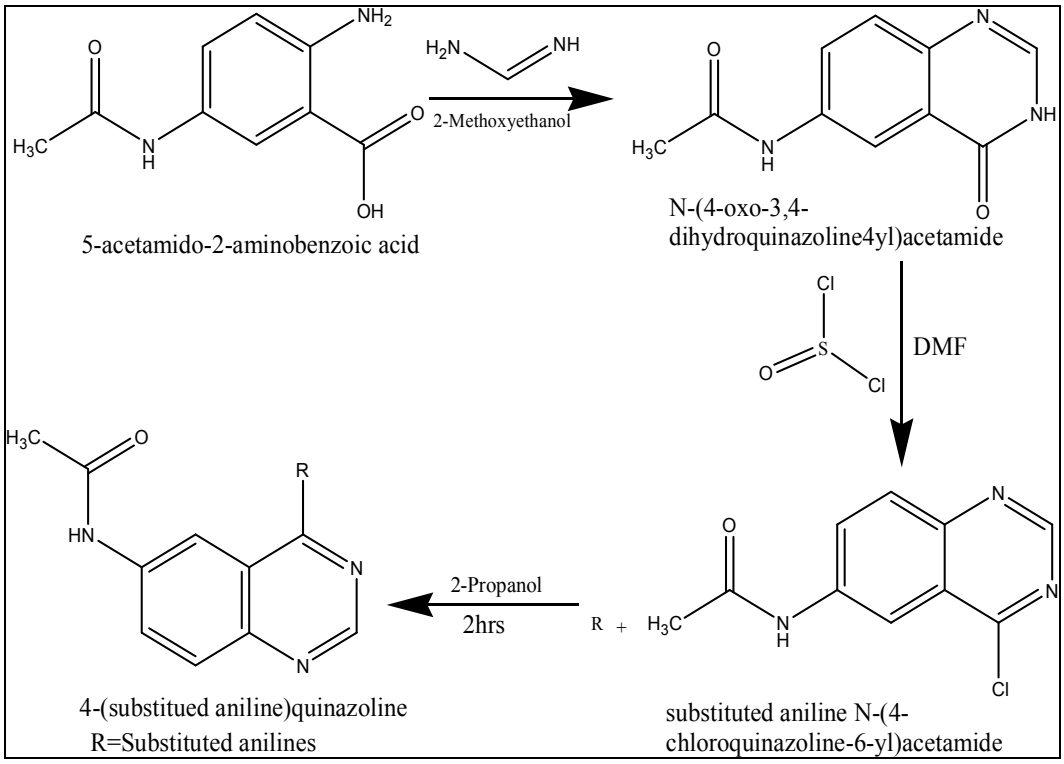
INTRODUCTION

An Antimicrobial is an agent that kills microorganisms or inhibits their growth. Microorganisms include a cellular entities, prokaryotic cells and eukaryotic cells. Today more than 60% drugs used in practice are synthetic derivatives and day by day the scope of synthetic research is broadening. Infectious disease, also known as transmissible disease or communicable disease is illness resulting from an infection. Infectious disease caused by things viruses, bacteria, fungi and parasites. In addition, emergence of microorganism resistant to antimicrobials to which these were previously sensitive to is cause of concern. Cases with such infections often fail to respond to the standard treatment, resulting in prolonged illness and increased risk of death. According to WHO, 440,000 new cases of multi-drug resistant tuberculosis (MDR-TB) emerge annually, causing at least 150,000 deaths. A more virulent form called extensively drug-resistant tuberculosis (XDR-TB) has been reported from 64 countries. Fungi are ubiquitous in the environment, and infection due to fungal pathogens has become more frequent. With the rise of HIV, opportunistic fungal pathogens have become a common cause of morbidity and mortality. However, about 43% of total deaths occurred in developing countries due to the infectious diseases in recent years [1].Fungal diseases represent a critical problem to health and they are one of the main causes of morbidity and mortality worldwide. Quinazoline itself (benzopyrimidine; 1, 3-benzodiazine) was prepared for the first time in 1903[2]. but its derivative was described even earlier by Greifs (1869). Quinazolines and its derivatives have attracted increasing attention due to numerous pharmacological applications including anticancer, anti-inflammatory, antibacterial, analgesic, antiviral, anticytotoxic, antispasm , antituberculosis , antioxidant , antimalarial . Quinazolines are more promising in case of anti-cancer activity, some quinazoline targeting protein tyrosine kinase and more selective compounds targeting EGFR, VEGFR and ERBB-2. Erlotinib and gefatinib are tyrosine kinase inhibitors acting on EGFR receptor used in non-small cell lung cancer, pancreatic cancer, adenocarcinoma and other types of cancer [3].

MATERIAL AND METHODS

All the chemicals used were purchased from commercial sources such as Alfa Aesar, SD fine chemicals and Spectrochem. Melting points were recorded on open capillary tube on super fit melting point

apparatus and uncorrected. The purity of all final compounds was assessed by TLC. TLC plates were visualized using UV lamp. IR spectra were recorded in KBr disk on "Shimadzu FTIR Model I.R Affinity" and reported in centimeters (cm-1). ^{1}HNMR spectra were recorded using ADVANCE II 400 NMR Spectrometer with tetramethylsline (TMS) as internal standard in DMSO.



Scheme-I: Scheme for synthesis of Quinazoline derivatives

N-{4-[(4-Chloro –3– nitro phenyl) amino] quinazoline-6-yl}acetamide (S1)
IR 3352 (NH),3070 (Ar CH), 3446 (N-H2 stretching), 1701 (C=O), 2953.02 (CH, ALIP), 1625.9 (C=N), 1HNMR (DMSO) $^{\delta}$ 10.632 (1H, S, NH-Ar), 8.353 (3H, m, Ar), 7.830 (2H, m, Ar), 7.814 (2H, d, Ar-NH), 2.119 (3H, m, CH3).

N-{4-[(4-Bromo –2– nitro phenyl) amino] quinazoline-6-yl}acetamide (S2)
IR 3072 for (NH), 3018 (CH-AR), 2694 (CH, ALIP), 1708 (C=O), 1HNMR (DMSO) $^{\delta}$10.589 (1H, S, NH-Ar), 8.201-8.231(6H, m, Ar), 7.808 (1H, m, Ar-NH), 2.116 (3H, S, CH3).

RESULTS

Antibacterial activity

The antibacterial activity was evaluated against the two gram negative cultures viz. *Escherichia coli, Salmonella typhi* and two gram positive cultures viz. *Staphylococcus aureus, Bacillus subtilis* using agar cup method, and results are shown as zone of inhibition (mm). Penicillin was used as a standard for synthesized compounds. Total 2 compounds were subjected.

Antibacterial activity by agar cup method

Escherichia coli:

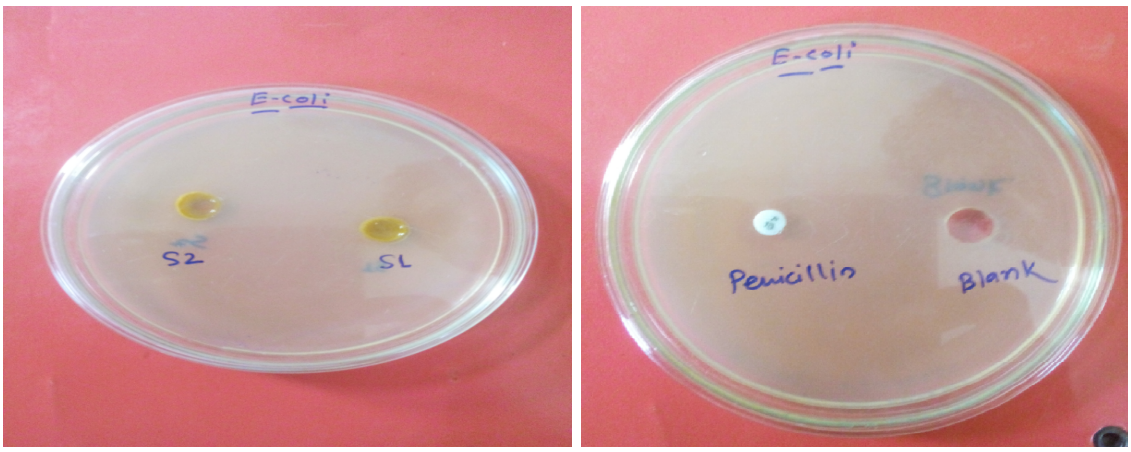


Figure 1: Zone of inhibition against *E. coli Salmonella typhi*

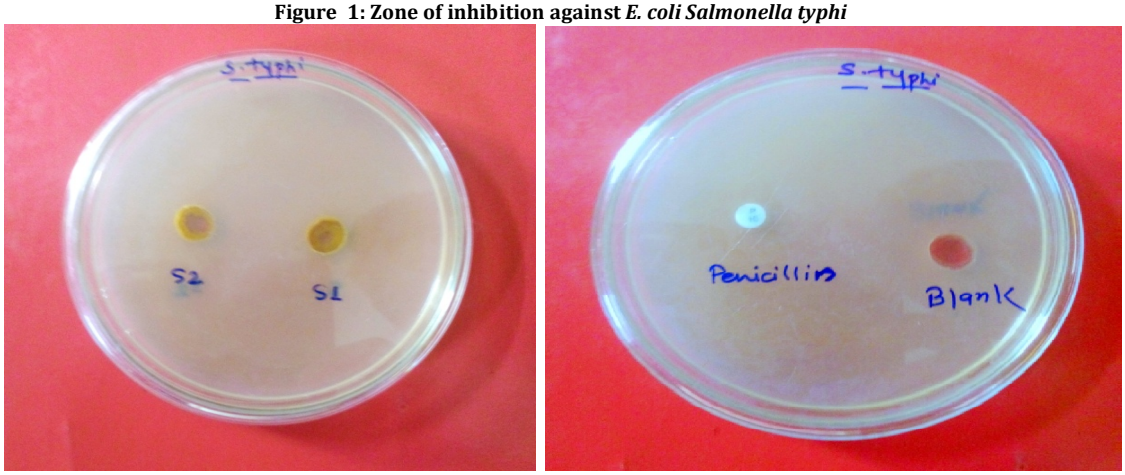


Figure 2: Depict the zone of inhibition against *S. typhi*

Staphylococcus aureus

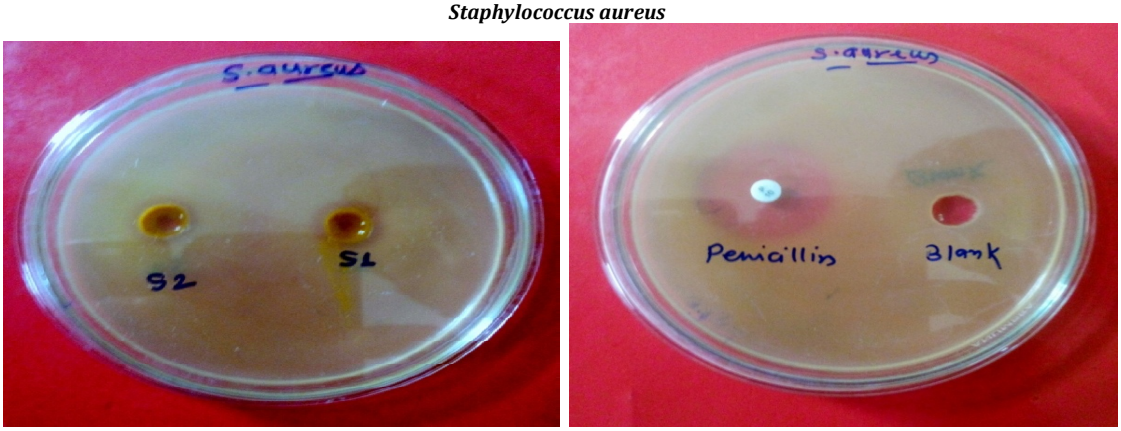


Figure 3: Depict the zone of inhibition against *Staphylococcus aureus*

Bacillus subtilis

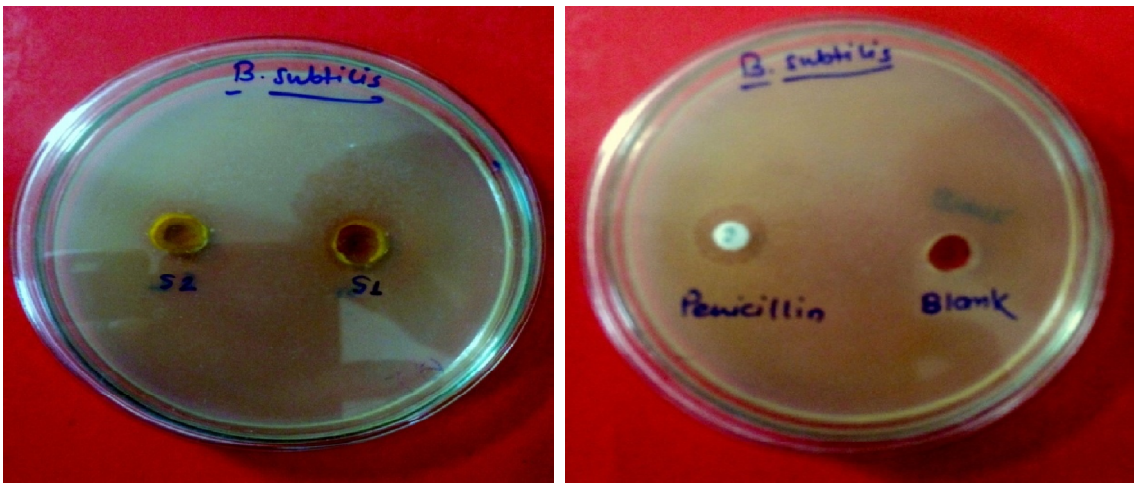


Figure 4: Depict the zone of inhibition against *Bacillus subtilis*

Table. No 1: Antibacterial activity of synthesized derivatives

Bacterial strain	Diameter of zone of inhibition (mean ± SEM in mm)		
	S1	S2	Penicillin
Escherishia coli	-	-	14.000 ± 0.5774**
Salmonella typhi	-	-	20.000 ±0.5774**
Staphylococcus aureus	12.000± 0.5774**	11.000 ± 0.5774**	36.000± 0.5774**
Bacillus subtilis	14.000 ± 0.5774**	14.000 ± 0.5774**	28.000 ± 0.5774**

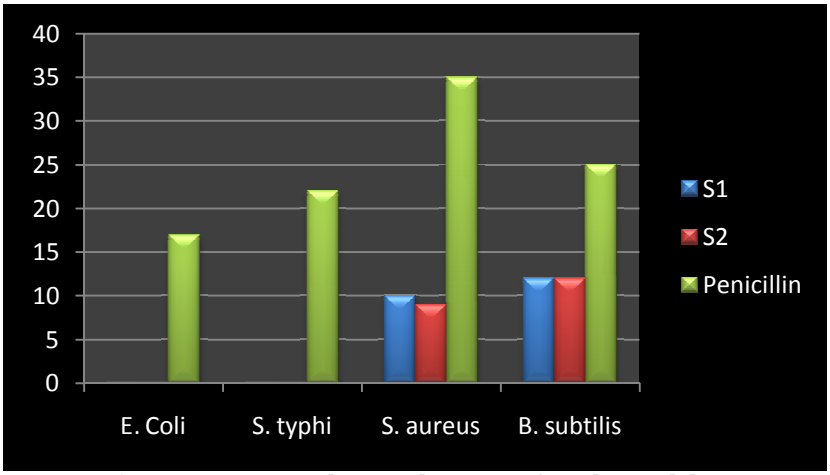


Figure 5: Comparative antibacterial activity of synthesized derivative

Both compounds were found inactive against *Escherichia coli and Salmonella typhi* as compared to Penicillin (14.000 ± 0.5774**) and (20.000 ±0.5774**) respectively.

The substitution, 4-chloro and 3-nitro in compound 1(S1) (12.000± 0.5774**), 4-bromo and 2-nitro in compound 2(S2) (11.000± 0.5774**), on 4-aminoqunazoline ring had shown no significant increase in the antimicrobial activity and these compounds found to be weak antibacterial agent against *Staphylococcus aureus* as compared to penicillin (36.000 ± 0.5774**).

When evaluated against *Bacillus subtilis* 4-chloro and 3-nitro in compound 1(S1) (14.000± 0.5774**), 4-bormo and 2-nitro in compound 2(S2) (14.000±0.5774**), on 4-aminoqunazoline ring had shown no significant increase in the antimicrobial activity and these compounds found to be weak but antibacterial agent as compared to penicillin (28.000 ± 0.5774**).

Antifungal activity[4-5]

The antifungal activity was evaluated against *Aspergillus niger, Penicillium chrysogenum, Fusarium moniliforme* and *Aspergillus flavus* using poison plate method, and results are shown in Table No. 6.5.1.3

as the growth of microorganism observed or not. The drug Griseofulvin was used as a standard for the synthesized derivatives.

Antifungal activity by poison plate method Compound 1 [S1]

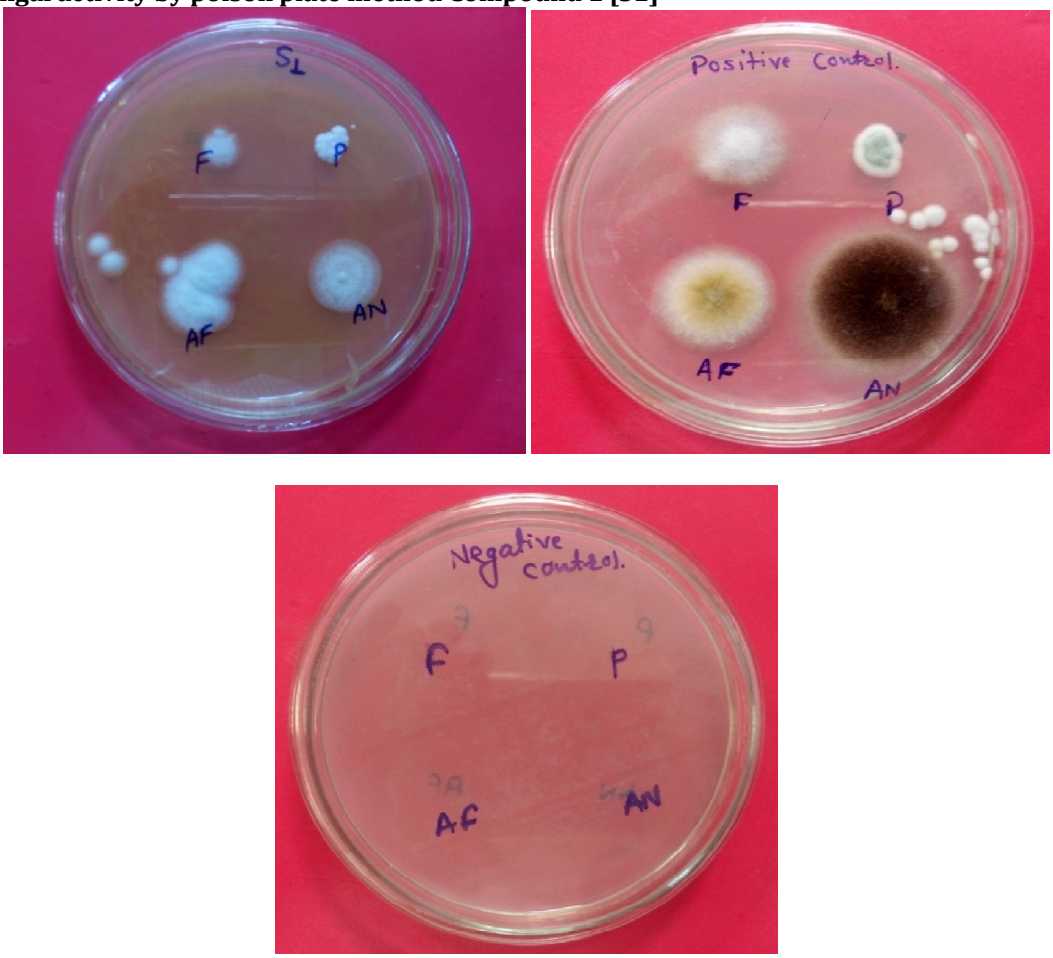
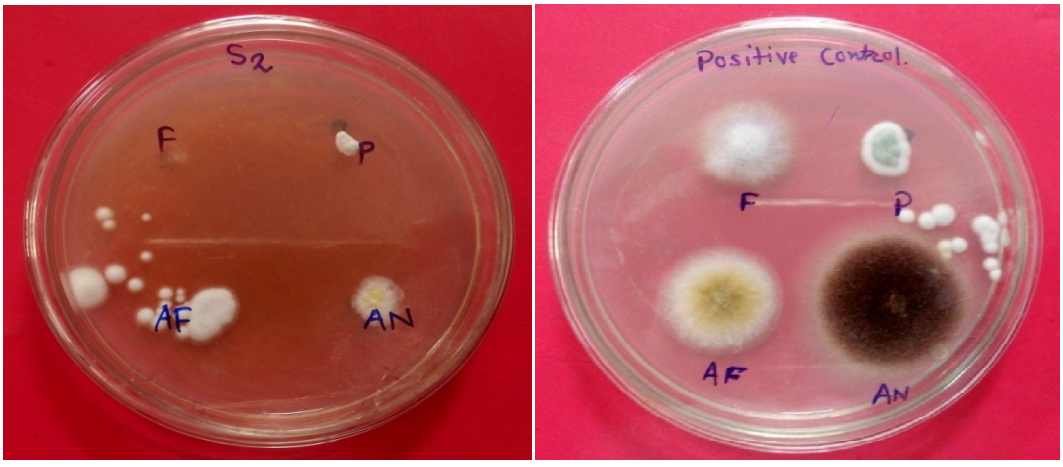


Figure 6 : Depict the antifungal activity of compound 1(S1)



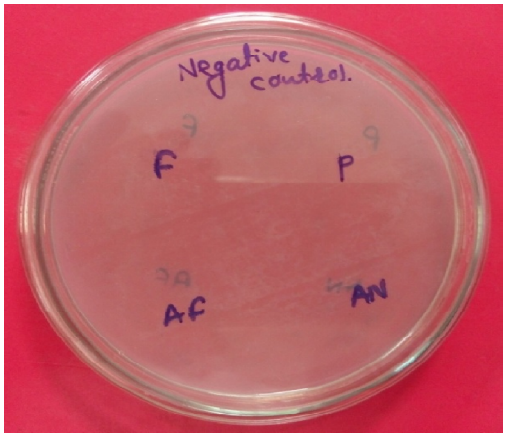


Figure 7 : Depict the antifungal activity of compound 2(S2)

Legends:
S1and S2 = Compounds 1and 2 (Test)
AN = *Aspergillus niger*
P = *Penicillium chrysogenum*
F = *Fusarium moneliforme*
AF = *Aspergillus flavus*
Griseofulvin = Standard

Table 2: Antifungal activity of synthesized derivatives

Sr.no	Compound	*Aspergillus niger*	*Penicillum chrysogenum*	*Fusarium moneliforme*	*Aspergill Us Flavus*
1	**S1**	**+ve**	**RG**	**RG**	**+ve**
2	**S2**	**RG**	**RG**	**-ve**	**+ve**
3	**DMSO (-ve control)**	**+ve**	**+ve**	**+ve**	**+ve**
4	**Griseofulvin (+ve control)**	**-ve**	**-ve**	**-ve**	**-ve**

Legends –
+ve = Growth (Antifungal Activity absent)
-ve = No Growth (More than 90% reduction in growth, Antifungal Activity present)
RG = Reduced Growth (More than 50% and less than 90 % reduction in growth, Antifungal Activity present

The substitution, 4-chloro and 3-nitro in compound 1(S1) on 4-aminoqunazoline ring had shown no activity against the *Aspergillus niger* and *Aspergillus flavus* but inhibit the growth (more than 50% but less than 90%) of *Penicillium chrysogenum* and *Fusarium moniliforme.*
The substitution, 4-bromo and 2-nitro in compound 2(S2), on 4-aminoqunazoline ring had shown the strong antifungal activity (90% inhibition) against *Fusarium moniliforme,* hence it is equipotent with griseofulvin, It had also shown inhibition of growth (more than 50% but less than 90%) of *Aspergillus niger* and *Penicillium chrysogenum* but inactive against the *Aspergillus flavus*

***In-vitro* anticancer activity[6-9]**

The synthesized compounds were subjected to preliminary testing for anticancer screening by using HeLa & MCF-7 cell line. Cell suspensions that were diluted according to the particular cell type and the cells were assayed by using the sulforhodamine B assay. Each drug is tested at 4 dose levels 10, 20, 40, 80µg/ml). Positive controls are run in each experiment and each experiment is repeated thrice. A plate reader was used to read the optical densities, and a microcomputer processed the optical densities into the special concentration in terms of GI50, TGI and LC50 values.

Human cervical malignant Cell Line [HeLa]

Table 3: *In-vitro* anticancer effect of compounds (S1 and S2) cell cervical malignant

Human cervical malignant Cell Line [HeLa]				
% Control Growth				
Drug Concentrations (µg/ml)				
	10	**20**	**40**	**80**
S1	105.6	103.1	88.8	-5.7
S2	106.9	103.2	83.0	-12.1
ADR	-42.2	-43.5	-40.5	-49.3

The graph shows the % control growth with different dilutions [10, 20, 40, 80 µg/ml]

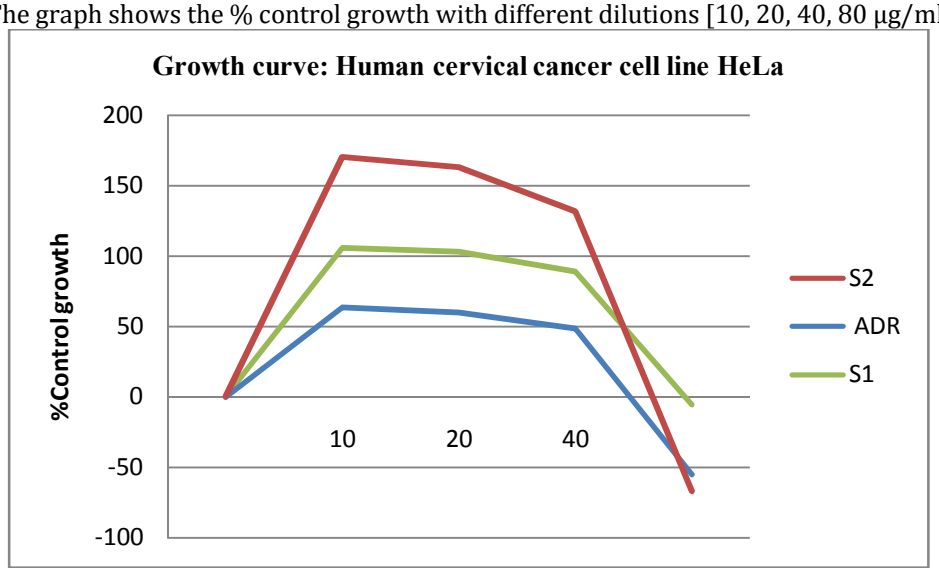


Figure 8 : *In-vitro* anticancer effect of compounds (S1 and S2) on HeLa cell cervical malignant

The following table shows LC50, TGI and GI50 of compounds against the HeLa cell line as compare to Adriyamycin as a standard.

Table 4 : *In-vitro* anticancer effect of compounds (S1 and S2) on LC_{50}, TGI, GI_{50} on HeLa cell cervical cancer.

HeLa	LC_{50}	TGI	GI_{50}
S1	**>80**	**81.8**	**51.4**
S2	**>80**	**77.5**	**49.0**
ADR	**<10**	**<10**	**<10**

Where,
LC_{50}=leathal concentration 50,
GI-Total growth inhibition,
GI_{50}-Growth inhibition.

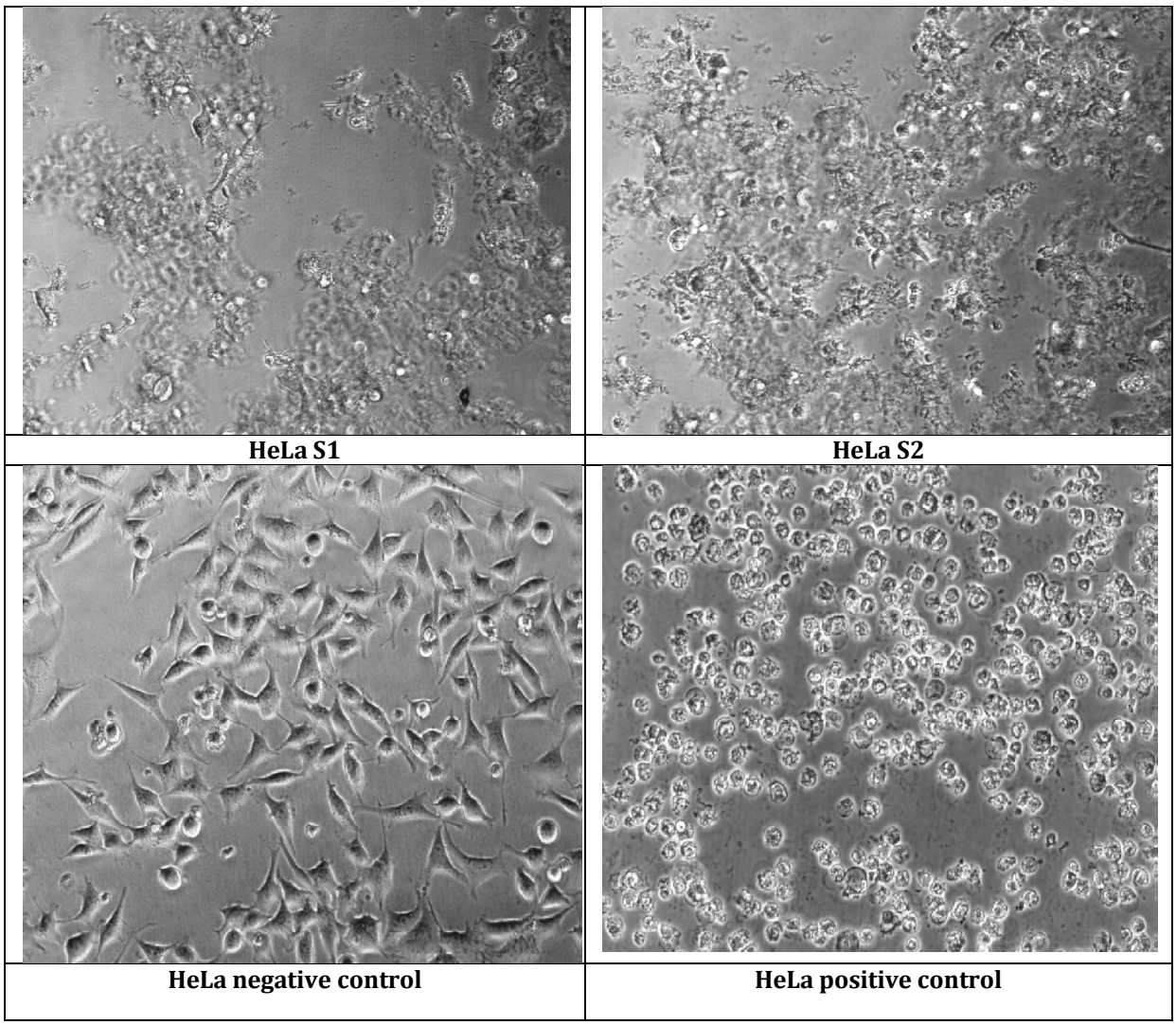


Figure 9: The anticancer effect of compounds (S1 and S2) cell cervical malignant or on HeLa cell

The following table shows LC50, TGI and GI50 of compounds against the MCF-7 cell line as compare to Adriyamycin as a standard

Table 5: *In-vitro* anticancer effect of compounds (S1 and S2) on MCF7 cell line.

Human breast cancer cell line MCF7				
% Control Growth				
Drug Concentrations (µg/ml)				
	10	20	40	80
S1	106.3	91.6	68.3	24.2
S2	99.0	90.0	53.2	-50.9
ADR	-46.0	-43.9	-59.0	-67.7

The graph shows the % control growth with different dilutions [10, 20, 40, 80 µg/ml]

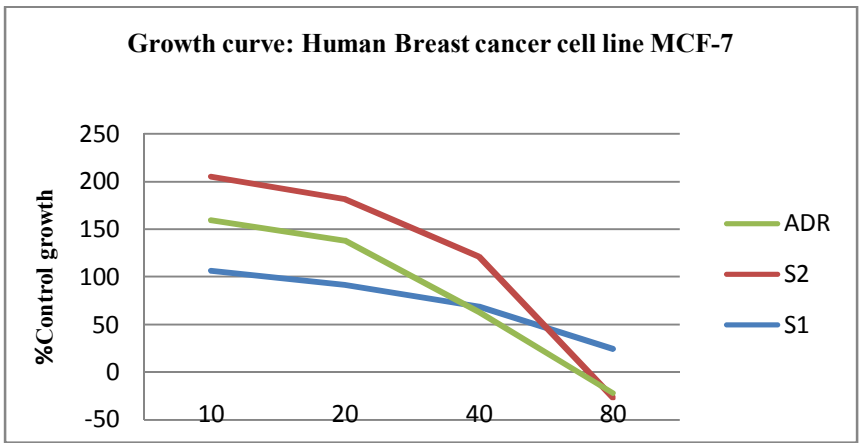


Figure 10: *In-vitro* anticancer effect of compounds (S1 and S2) on HeLa cell cervical malignant

Table 6: *In-vitro* anticancer effect of compounds (S1 and S2) on LC50, TGI, GI 50 in MCF7 cell breast cancer

MCF-7	LC50	TGI	GI50
S1	>80	>80	57.0
S2	82.0	59.2	36.5
ADR	25.5	NE	<10

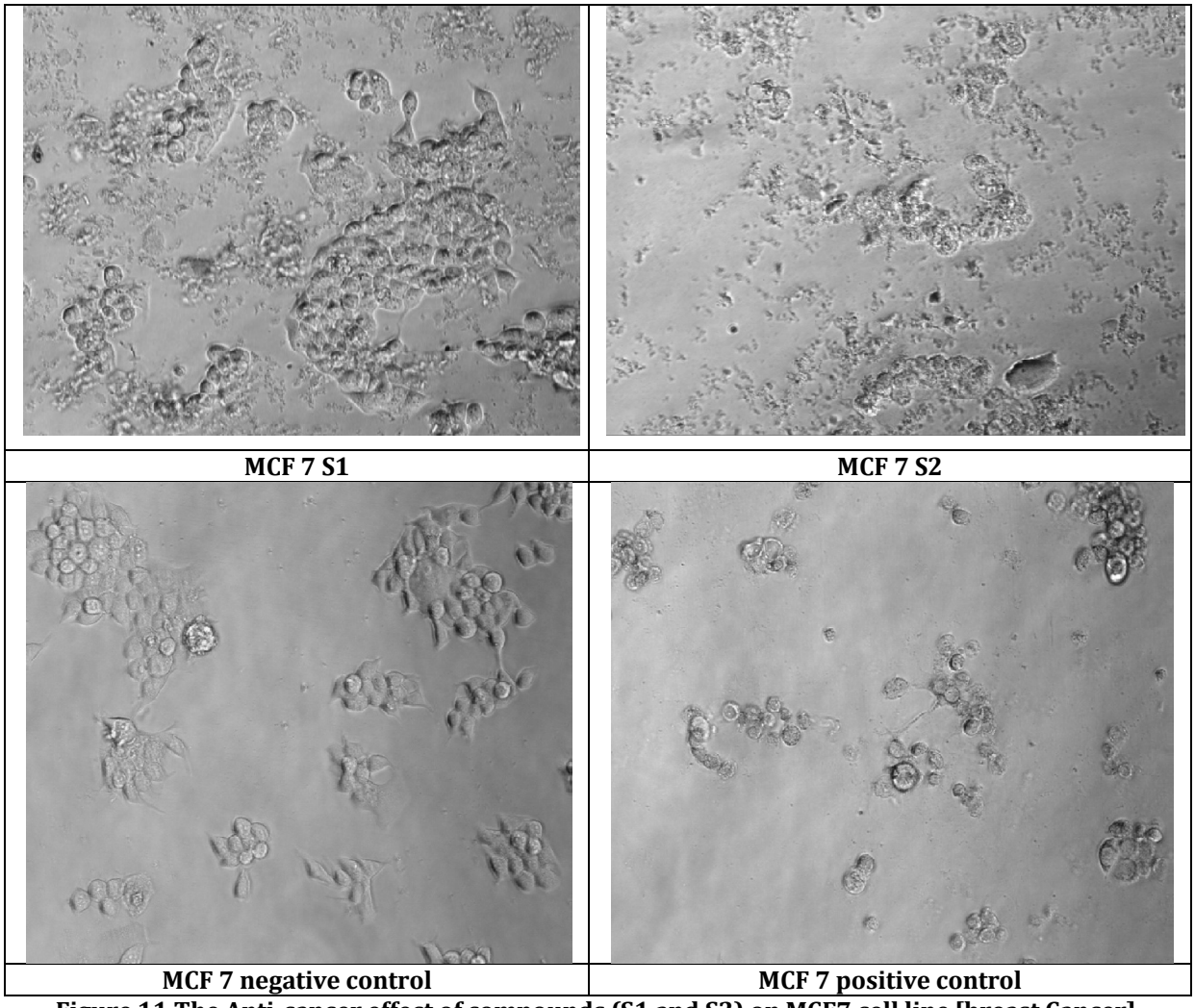


Figure 11 The Anti-cancer effect of compounds (S1 and S2) on MCF7 cell line [breast Cancer].

The anticancer activity of all the synthesized compounds (S1and S2) was evaluated against HeLa and MCF-7 cancer cell lines using SRB method and the GI50 values of all the compounds including the intermediate were shown in Table (HeLa) and (MCF-7).Both the synthetic compounds produced a dose dependant inhibition of growth of the cells. The GI50 values of S1 the synthetic test compounds were found to be 51.4 and 57 respectively against HeLa and MCF-7 cell. The GI50 values of S2 the synthetic test compounds were found to be 49 and 36.5 respectively against HeLa and MCF-7 cell. The GI50 of these compounds were comparable with known anticancer agent Adriyamycin (GI50 value <10). The present study reveals that among the human cancer cell lines tested, HeLa cells are slightly more sensitive to all the tested compounds than MCF-7 cells. Many anticancer drugs are effective against HeLa and MCF-7 cells by causing apoptosis through the expression of caspase-3, generating reactive oxygen species (ROS) and damaging DNA (Leong et al., 2003).Cisplatin causes cytotoxicity in MCF-7 and HeLa cells by a similar mechanism. Results indicate that the anticancer or cytotoxicity of derivatives varied with structural modification.

Structural evaluations of synthesized compounds [23-27]

After synthesis of new compounds it is identified by means of physical and chemicals parameters like melting points, boiling points, solubility, chemical tests, elemental analysis etc. other analytical methods like TLC, UV, IR, NMR spectroscopy were also applied in characterization of newly synthesized compounds a brief outline is given below.

Infrared Spectral Studies

Infrared spectroscopy is one of the important tools for detecting the various functional groups and possible chemical structure. The important advantages of IR over the other technique is that it gives fingerprints (4000-400 cm-1) information about the structure (functional group, bonding with each other) of molecules easily. No two compounds have identical fingerprint region. This technique is based upon the molecular vibration of the compound in which each and every bond vibrates at the different frequencies and this vibration frequency corresponds to the IR frequency.

Thus IR spectra of each and every bond are formed. IR spectra were recorded in KBr on "Shimadzu FTIR model I.R affinity" and reported in cm-1.

Nuclear Magnetic Resonance

The interaction between matter and electromagnetic forces can be observed by subjecting a substance simultaneously to magnetic forces, one stationary and other varying at some radio frequency. At a particular combination of fields, energy is absorbed by the sample and absorption can be observed as a change in signal developed by radio frequency detector and amplifier. This energy f absorption can be related to a magnetic dipolar nature of the spinning nuclei. This technique is useful in assuming the structure of molecule. Synthesized compounds were subjected to 1HNMR spectral studies on the: Model "BRUKERAVANCE II400 NMR spectrometer".

Antibacterial Activity [9-14]

The antibacterial activity of synthesized compounds was measured by screening them against the two gram negative cultures viz. *Escherichia coli, Salmonella typhi* and two gram positive cultures viz. *Staphylococcus aureus, Bacillus subtilis* using agar cup method. The basic principle of microbial assay lies in the comparison of inhibition of growth of microorganism produced by the known concentration of antibacterial agent to be tested with that produced by known concentration of standard antibacterial agent having known activity.

Antifungal Activity[15-22]

The antifungal activity of synthesized compound was determined by screening them against the *Aspergillus Niger*, *Penicillium chrysogenum*, *Fusarium moneliforme*, *Aspergillus flavus* using poison plate method. The basic principle of antifungal assay lies in the comparing whether there is growth of microorganism observed on unknown test compounds media plate compared with that of standard media plate. If growth observed then compound does not possess antifungal activity.

***In-vitro* Anticancer Screening**

Screening assay procedure

The synthesized compounds were subjected to preliminary testing for anticancer screening by using HeLa & MCF-7 cell line. Cell suspensions that were diluted according to the particular cell type and the cells were assayed by using the sulforhodamine B assay. Each drug is tested at 4 dose levels 10, 20, 40, 80µg/ml). Positive controls are run in each experiment and each experiment is repeated thrice. A plate reader was used to read the optical densities, and a microcomputer processed the optical densities into the special concentration in terms of GI50, TGI and LC50 values.

Screening Procedures

Cell suspensions that were diluted according to the particular cell type and the expected target cell density (5000-40,000 cells per well based on cell growth characteristics) were added by pippet (100 µL)

into 96-well microtiter plates. Inoculates were allowed a preincubation period of 24 h at 37° C for stabilization.

Table 7:Special Concentration Parameters (GI_{50}, TGI, and LC_{50})

GI_{50}	Growth inhibition of 50 % (GI50) calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50 drug concentration resulting in a 50% reduction in the net protein increase. The GI50 measures the growth inhibitory power of the test agent.
TGI	Drug concentration resulting in total growth inhibition (TGI) will calculate from Ti = Tz The TGI signifies a cytostatic effect.
LC_{50}	Concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of 50% cells following treatment is calculated from [(Ti-Tz)/Tz] x 100 = -50. The LC50, which signifies a cytotoxic effect
ADR	Adriyamycin, Positive control compound.

Ti = the optical density of the test well after a 48hrs period of exposure to test drug.
Tz = the optical density at time zero is T0
C = the control optical density.
Dilutions at twice the intended test concentration were added at time zero in 100µL aliquots to the microtiter plate wells. Usually, test compounds were evaluated at five 10-fold dilutions. In routine testing, the highest well concentration is 10E-4 M, but for the standard agents the highest well concentration used depended on the agent. Incubations lasted for 48 hrs in 5% CO2 atmosphere and 100% humidity. The cells were assayed by using the sulforhodamine B assay. A plate reader was used to read the optical densities, and a microcomputer processed the optical densities into the special concentration parameters defined later.

DISCUSSION

The newly synthesized compounds were screened for their *In-Vitro* antimicrobial activity against bacteria's such as *Escherichia coli, Salmonella typhi Bacillus subtilis* and *Staphylococcus aureus*. Both modified compounds were found inactive against *Escherichia coli, Salmonella typhi, Bacillus subtilis* and *Staphylococcus aureus* as compared to Penicillin respectively. The substitution, 4-chloro and 3-nitro in compound 1(S1) on 4-aniloqunazoline ring had shown no activity against the *Aspergillus niger* and *Aspergillus flavus* but inhibit the growth (more than 50% but less than 90%) of *Penicillium chrysogenum* and *Fusarium moniliforme.* The substitution, 4-bromo and 3-nitro in compound 2(S2), on 4-aniloqunazoline ring had shown the strong antifungal activity (90% inhibition) against *Fusarium moniliforme,* hence it is equipotent with griseofulvin, It had also shown inhibition of growth (more than 50% but less than 90%) of *Aspergillus niger* and *Penicillium chrysogenum* but inactive against the *Aspergillus flavus.* The compounds were submitted to screen for their anticancer potential at ACTREC on the basis of results obtained it was found that N-{4-[(4-chloro-3-nitrophenyl) amino] quinazoline- 6-yl} acetamide and N-{4-[(4-bromo-2-nitrophenyl) amino] quinazoline-6-yl} acetamide these two compounds didn't show any expected anticancer activity on MCF and HeLa cell line. Modification in the lead molecule via different stages changes the structural variation gave the new ideas for the further investigation on quinazoline derivatives.

CONCLUSION

On the basis of data obtained from the study, we concluded that the tested quinazoline derivatives had failed to produce antibacterial activity against the gram negative strains but possess the weak antibacterial activity against the gram positive strains. The antibacterial activity can be improved by substitution by halogens such as fluorine or iodine group. In other hand, the substitution, 4-bromo and 3-nitro in compound 2(S2), on 4- aniloqunazoline ring had shown the strong antifungal activity (90% inhibition) against *Fusarium moniliforme,* hence it is equipotent with griseofulvin. These compound suggesting that it could be useful in the treatment of fungal infection. Further studies will be required to explore precise mechanisms and component underlying these beneficial biological effects. The desire compounds had no anticancer effect but percentage growth inhibition was increased with increasing the dilutions. Further investigation is warranted, with altered substitution to observe its effects on anticancer potential.

CONFLICT OF INTEREST

The authors have declares that no competing interest exists.

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