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SYNTHESIS & INVITRO ANTICANER & ANTI-MICROBIOLOGICAL EVALUATION OF SOME AMINE SUBSTITUTED QUINAZOLINE DERIVATIVES

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ABSTRACT

The quinazoline derivatives have drawn more and more attention in the past few years owing to its significant biological activity. The biological activities and synthesis have led to its use and investigation for more and more derivatives. For various physiological significant and pharmacologically utilized molecules quinazoline is considered as the main pharmacophore. It exhibits a broad spectrum of biological activities such as anti-infllamatory, anticancer, anti-HIV, antifungal, antibacterial, anticoccidal, anticonvulsant, antidepressant, antimalerial. As it shows many activities the alteration are done with different substitutes.Thus our main aim is to focus on synthesis, and to determine physiological constants, and pharmacologically evaluate the amine substituted quinazoline derivatives.

KEYWORDS: Quinazoline, biological activities, anticancer.

1.0. INTRODUCTION

Quinazoline are a class of fused heterocyclic compound that consist of diversified biological properties. Many quinazoline derivatives are used which shows activities like anti cancer, antimicrobial, antimalerial, anti-fungal, antitubercular, diuretic, muscle relaxant, antiviral, antiprotozoan, antidepressant, weedicide, and much more. Quinazoline is also used preparation of various functional materials for synthetic chemistry and also present in various drugs molecules.[1]

2.0. MATERIALS AND METHODS

The chemicals used in the study were procured from LOBA Chemie and E. Merck. The reactions were monitored using silica Gel G. The determination of melting point were done using open glass capillary using Kjeldahl flask containing liquid paraffin.

3.0. SYNTHESIS OF QUINAZOLINE DERIVATIVES

STEP 1: Synthesis of Quinazolin-4-ol (I):

A mixture of anthranilic acid (13 gm, 94.7mmol) was heated with formamide (42 gm, 94.7mmol) in absolute ethanol at 65º C for 4 hrs. it was then cooled at room temperature. The mixture solidified. It was broken up and mixed with water and then filtered. The residue was then crystallized from ethanol to afford pure compound [I].

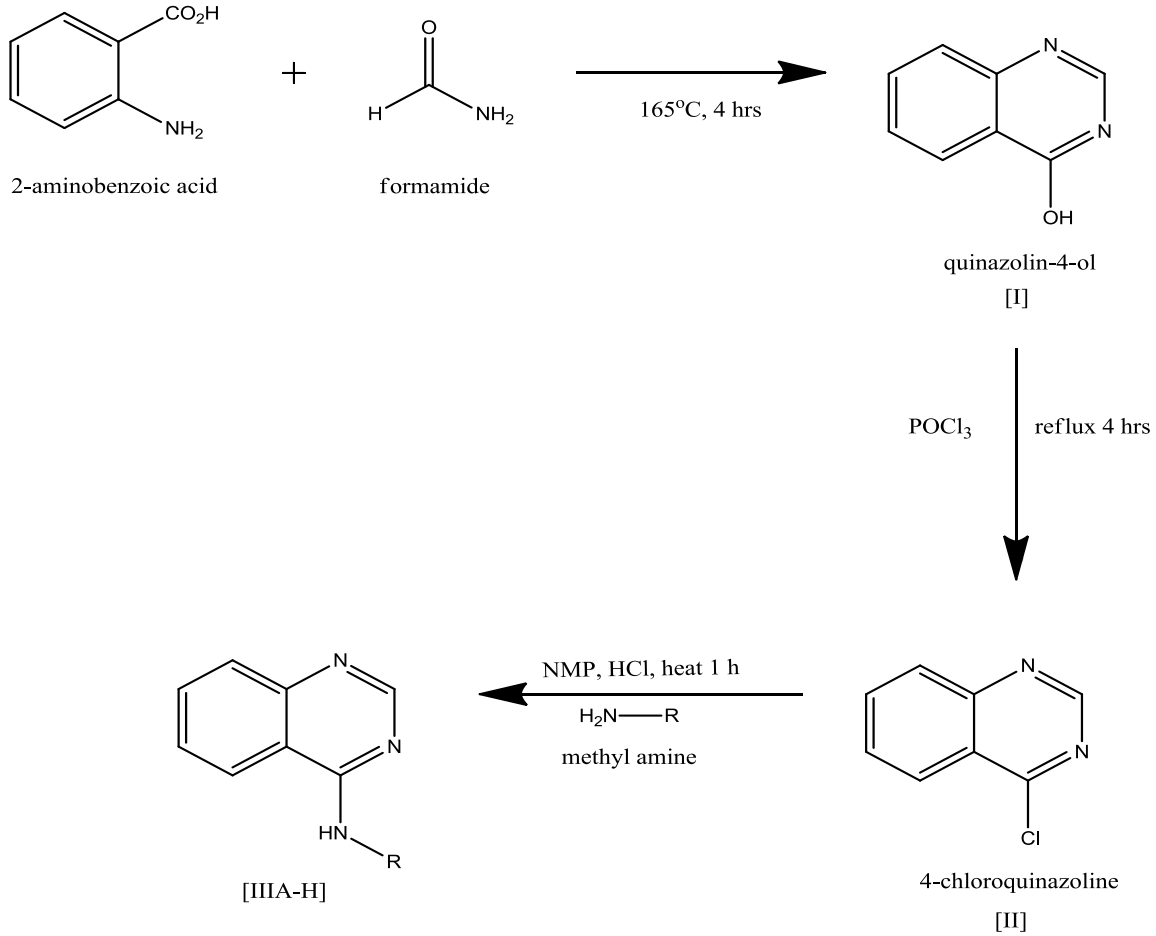
STEP 2: Synthesis of 4-chloroquinazoline (II):

The quinazoline-4-ol (9 gm) was dissolved in 50 mL $POCl_3$ in a round bottom flask. Heat it at oil bath 120º C for 4 hr. when the solid was dissolved it was again heated for 1 hr.under reduced pressure the volatile materials were removed. The viscous oily mass was added continuously to ice-cold liquid ammonia. The precipitated materials were filtered and extracted with petroleum ether. Recrystallize the solid using petroleum ether respectively to afford pure compound [II].

STEP 3: Synthesis of 4-yl-amino-quinazoline derivatives (IIIa-h):

Compound 4-chloroquinazoline (8 gm, 48.7 mmol) was dissolved in 20 mL of N-methyl-pyrrolidine (NMP) and substituted amine (5.9gm 48.7mmol) was added to this solution. Reaction mixtures were heated at 60 ºC and after that 4 drops of conc. HCl were added and reaction mixture was heated for 1 hr. Separate and filter the precipitate by recrystallization from ethanol, thus the yielded product is the pure compound [IIIa-h].[2-9]

4.0. SCHEME



4.1. FOR COMPOUND A TO H:

COMP. CODE	R	COMP. CODE	R
A	H_3C—	**E**	CH_3
B	H_3C	**F**	
C	H_3C CH_3	**G**	
D	CH_3	**H**	

5.0. ANTI-CANCER EVALUATION OF SYNTHESIZED COMPOUNDS: [10-11]

5.1. Drugs and chemicals: Cyclophosphamide (Endoxan®) was obtained from German Remedies, Mumbai. And the other chemicals anthranilic acid, formamide, $POCl_3$, NMP, HCl, ethanol, petroleum ether, methylamine, ethylamine, isopropylamine, amylamine, cyclohexylamine, cyclopropylamine, napthylamine, n-propylamine were of A.R. grade, obtained from LOBA Chemie. Saline water (Claris Life sciences Ltd., Ahmedabad) was obtained from drug store.

5.2. Culture and cell lines: HL-60 cell line And the Agrobacterium tumefaciens(ATCC-33970) stock culture was procured from National Chemical Laboratory, Pune.

5.3. POTATO DISC ASSAY

Fresh potatoes were obtained and sterilized using 20% bleach solution. Wash it with cold water, peel and immersed in bleach solution (10%) for 2 mins. Test solution was prepared in dilutions of 0.5mg/ml, 0.05mg/ml and 0.01mg/ml in sterile water using acacia as suspending agent. Similarly, standard solution of cyclophosphamide was prepared of same dilutions. A control solution was prepared which contains 5% acacia in sterile water. Potatoes rinsed with water, and cut into rectangular blocks (1×1 cm), soak it in sterile water for 20 mins. Culture plates containing 1 mL 1.5% agar solution was prepared and potato discs transferred in to the culture plates at the center of the wells. Using sterile micropipette 400 µL bacteria solution was combined with 400 µL of the appropriate test, standard or control solution in test tubes. Each potato disc was inoculated with 1 drop (50 µL) of the test, standard or control solution within 30 min after placing in wells. Plates covered and lids were tightened using parafilm to reduce moisture loss and incubated under dry conditions at room temperature for 7-12 days. After incubation period, potato discs were stained with Lugol's solution and analyzed for staining using dissecting microscope under 10X magnification. Tumors lack starch and turned orange and normal discs stained dark blue colored. The percentage inhibition was calculated using

$$\text{Percentage inhibition} = 100 - \frac{\text{Average No.of tumors observed in test}}{\text{Average No.of tumors observed in control}} X\ 100$$

5.4. ONION ROOT TIP ASSAY

Onions were allowed to grow under the tap water for 24 hrs. Sample solutions were prepared by dissolving known weight of test compound in propylene glycol (1ml) and dilute it with distilled water (9ml). A series of test tube was prepared 100µg, 200µg and 300µg/ml. Standard solution of cyclophosphamide were also prepared in the same way. Remove the old roots and immerse the onion base to an extent of about 0.5 cm in a sample tube containing the sample solution for two days for germination. After that the germinated root tips were removed and placed in the sample tube containing the fixing solvent (ethanol-acetic acid, 3:1 v/v). After 24 h, the fixing solvent was decanted and the root tips were washed with the preservative solvent (70% alcohol). Similarly onion roots were also allowed to germinate in a control solution (Distilled water). Root tips were placed on a clean watch glass containing staining solution [1 g of orcein in 45% of acetic acid: 0.2 N HCl (7:1 v/v)] and heated on the flame until fumes come out. Cool under room temperature and placed on a micro slide, a drop of stain solution added and tips were squashed by a blade. The slide was mounted for observation under a microscope (45X). The number of dividing cells and total number of cells were counted. The percent of the number of dividing cells compared to the control and the percent inhibition of mitosis by the sample against control were calculated.

Mitotic index was calculated by following equation:

$$\text{Mitotic index} = \frac{\text{NO.of dividing cell}}{\text{Total No. of cell}} \text{ x } 100$$

5.5. TRYPAN BLUE ASSAY

HL-60 (Human promyelocytic leukemia) cell culture was obtained from National Center for Cell Science, Pune, India. Grow at 37°C and humidified at 5% CO_2 in RPMI 1640 medium, filtered using 0.45 µm membrane filter. Concentrations from 1-1000 µg mLG1 were prepared by dissolving known weight of sample in acacia. Similarly the standard solution was prepared containing the same concentrations of cyclophosphamide, also 10 mL acacia served as control solution. Placed 0.5 mL of a suitable cell suspension (dilute cells in complete medium without serum to an approximate concentration of 1×105 to 2×105 cells per mL) in a T-shaped flask and add 0.1 mL of 0.4% trypan blue stain (Merck Ltd., Mumbai), mixed thoroughly and allowed to stand for anticancer activity.

$$\%\ \text{cell viability} = \frac{\text{Total No.of cells}}{\text{Total No.of cell}} X\ 100$$

6.0. MICROBIOLOGICAL SCREENING

6.1. ANTI-BACTERIAL ACTIVITY[12-13]

6.1.1. Method: Cup-plate agar diffusion method using Nutrient agar.

Radial or 2D technique, Melted agar previously inoculated with selected microorganism was poured in a petri plate. After solidification, with the borer make the cups and fill it with solution of suitable concentrations of sample and standard respectively, inoculate it at 37°C for 24 hours. The zone of inhibition can be seen as the antimicrobial agent diffuses through the agar around

6.1.2. Materials Used

1) Culture: Two G +ve and one G -ve organism was chosen for screening

Gram positive organisms: *Staphylococcus aureus* (ATCC 29737) and *Bacillus subtilis* (ATCC 6633)

Gram negative organism: *Escherichia coli* (NCTC 10418)

2) Apparatus: Sterile Petri plates, cotton swabs, cork borer, test tubes, 1mL syringes, Micropipette, inoculating loop and spirit lamp

3) Media: Nutrient agar media from Hi-Media was used with composition:

Peptic digest of animal tissue	5.00 gm/lt.
Sodium chloride	5.00 gm/lt.
Beef extract	1.50 gm/lt
Yeast extract	1.50 gm/lt.
Agar	15.00 gm/lt

Dissolve 28gm of media in 1000ml of distilled water by heating, sterilize it by autoclaving at 121°C temperature and 15 Ib/Inch^2 pressure for 15 minutes.

c) Preparation of Inoculums
One day prior, inoculations of the above bacterial cultures were made in the Nutrient agar media and incubated at 37°C for 18-24 hrs.

d) Preparation of test solutions
Each test compound (2 mg) was dissolved in dimethylformamide (5 mL) to give stock solution of concentration 200 µcg/mL. Then 0.1 mL of this solution was used for testing.

e) Preparation of standard solution
Ciprofloxacin was used as standard drug at the concentration of 200µcg/mL

f) Method of testing
Nutrient agar plates were prepared by pouring 15-20ml of the medium.

Nutrient agar plates were prepared by pouring 15-20 mL of the medium into each sterilized Petri dish and were allowed to cool at room temperature. The standardization of the cell sample was done at the density of 530nm using spectrophotometer and inoculated at the surface of the agar medium. With the sterile borer the cups of 6 mm in diameter was made.

Using micropipettes, the test solution (0.10ml) was added in cups and incubate the petri plates at 37°C for 48 hrs. for each organism the zone of inhibition was measured in mm.

g) Observation
Plates were observed within 20 to 24 hours and may be continued to incubate for 48 hours. The zone of inhibition was observed, measured and compared with the standard compound.

6.2. ANTI-FUNGAL ACTIVITY[14-15]
6.2.1. Method: Cup-plate agar diffusion method using Nutrient agar.

6.2.2. Materials Used
1. **Test organisms:** *Candida albicans* (NCIM 3102), *Aspergillus niger* (NCIM 596).
2. Sterile Petri plates, sterile cotton swabs, sterile cork borer, sterile test tubes, 1mL syringes, Micropipette, Inoculating loop and Spirit lamp.

1) Media: Sabouraud-Dextrose agar media was used with composition:

Mycological peptone	10.00 gm/lt
Dextrose	40.00 gm/lt.
Agar	15.00 gm/lt

c) Preparation of Sub-culture
Inoculate the fungal cultures one day prior to testing in the Sabouraud-Dextrose agar and incubate it at 37°C for 18-24 hrs. A suspension of cell from this culture was made in sterile distilled water. Five colonies of >1mm diameter were mixed with 5 mL of normal saline and vortexed for 15 sec.

d) Preparation of test solutions
Each test compound (10 mg) was dissolved in 5mL of dimethylformamide to give stock solution of concentration 2000 µcg/mL. Then 0.1 mL of this solution was used for testing.

e) Preparation of standard solution
Standard drug Griseofulvin was used. The concentration was 200µcg/mL.

f) Method of testing
Sabouraud-Dextrose agar plates were prepared by pouring 15-20 mL of the medium into each sterilized Petri dish and were allowed to set at room temperature.

The standardization of the cell suspension was done to a density of 530nm using spectrophotometer, and inoculate over the surface of the medium. Using a sterile cork borer 3 cups were scooped in each plate. Test solution (0.10 mL/0.15 mL) was added in the cups and then incubated at 37°C for 48 hrs. The zone of inhibition was measured in mm for each organism.

g) Observation
Plates were observed within 20 to 24 hours and may be continued to incubate for 48 hours. Zone of inhibition of the compound discs were measured and compared with the standard compound discs.

7.0. RESULTS AND DISCUSSION
The table no. 1 contains the synthesized new compound's structures, yields, and melting points. The sharp melting point of the synthesized compounds indicates that the compound is pure. The yield value of the compounds also suggested that the chemical methods were reliable for the synthesis of the compound. The spectral data were also in accordance with the assumed structure. All the synthesized compounds were screened for their antibacterial, antifungal activity using ciprofloxacin and griseofulvin as standard drug.

Table no. 1: Analytical & Physicochemical data of the synthesized compounds (A to H).

Comp.	Mol. Formula	Mol. Wt. (gram)	M.P. (° C)	% Yield	Elemental analysis Calculated		
					C	H	N
A	$C_9H_9N_3$	159.19	110	77	67.90	5.70	26.40
B	$C_{10}H_{11}N_3$	173.21	114	75	69.94	6.40	24.26
C	$C_{11}H_{13}N_3$	187.24	112	71	70.56	7.00	22.44
D	$C_{13}H_{17}N_3$	215.29	117	76	72.52	7.96	19.52
E	$C_{11}H_{13}N_3$	187.24	115	69	70.56	7.00	22.44
F	$C_{11}H_{11}N_3$	185.23	114	66	71.33	5.99	22.69
G	$C_{14}H_{17}N_3$	227.30	113	71	73.98	7.54	18.49
H	$C_{18}H_{13}N_3$	271.32	119	69	79.68	4.83	15.49

8.0. SPECTRAL DATA OF SYNTHESIZED COMPOUNDS A-H:

A: FT-IR (KBr disc) cm^{-1} : 1246.33 (C-N str.), 3344.12 (NH str.), 3039.84 (Arm CH), 2962. 74 (Alk CH), 1768 (C=C); **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.58-8.49 (5H) Quinazoline, 4.0 NH amine, 2.78 (3H) of CH_3.

B: FT-IR (KBr disc) cm^{-1} : 1326 (C-N str.), 3020.93 (NH str.), 2962 (Arm CH), 2869 (Alkenyl CH), 1665.05 (C=C), **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.58-8.49 (5H) Quinazoline, 4.0 NH amine, 1.14 (2H) CH_3, 3.47 (3H) CH_2.

C: FT-IR (KBr disc) cm^{-1} : 1248.68 (C-N str.), 3313.02 (NH str.), 3034.30 (Arm CH), 2955.17 (Alk CH), 1767.92 (C=C); **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.58-8.49 (5H) Quinazoline, 4.0 NH amine, 3.95 (6H) CH, 1.07 (H) CH_3.

D: FT-IR (KBr disc) cm^{-1} : 1306.41 (C-N str.), 3045.95 (NH str.), 2961.63 (Arm CH), 2871.56 (Alk CH), 1673.21 (C=C); **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.58-8.49 (5H) Quinazoline, 4.0 NH amine, 0.90 (2H) CH_3, 1.31-3.20 (8H) CH_2.

E: FT-IR (KBr disc) cm^{-1} : 1388.27 (C-N str.), 3045.15 (NH str.), 2963.32 (Arm CH), 2926.39 (Alk CH), 1672.39 (C=C); **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.58-8.49 (5H) Quinazoline, 4.0 NH amine, 1.57 (5H) CH_2, 3.10 (2H) CH_2, 0.90 (2H) CH_3.

F: FT-IR (KBr disc) cm^{-1} : 1370.32 (C-N str.), 3046.24 (NH str.), 2960.17 (Arm CH), 2869.32 (Alk CH), 1673 (C=C); **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.58-8.49 (5H) Quinazoline, 4.0 NH amine, 1.35 (4H) CH, 0.55-0.80 (4H) CH_2.

G: FT-IR (KBr disc) cm^{-1} : 1343.60 (C-N str.), 3044.20 (NH str.), 2964.62 (Arm CH), 2875.81 (Alk CH), 1670.02 (C=C); **^{1}H-NMR (δ ppm): (400 MHz, DMSO):** 7.58-8.49 (5H) Quinazoline, 4.0 NH amine, 1.21-2.57 (11H) C_6H_{11}.

H: FT-IR (KBr disc) cm^{-1} : 1386.47 (C-N str.), 3043.96 (NH str.), 2962.42 (Arm CH), 2875.65 (Alk CH), 1672.04 (C=C); **^{1}H-NMR (δ ppm):** (400 MHz, DMSO): 7.58-8.49 (5H) Quinazoline, 4.0 NH amine, 6.98-8.07 (7H) C_9H_7.

Table.no. 2: Potato disc assay of amine substituted quinazoline derivatives.

Parameter	Conc mg/ml	Average no. of tumor observed	% inhibition
Control	-	80	00
Standard cyclophosphamide	0.01	10.352 ± 0.3333	87.06
A	0.50	18.00 ± 0.1235	77.50
	0.05	19.002± 1.0233	76.225
	0.01	22.76 ± 0.0448	71.55
B	0.50	25.41 ± 1.0551	68.23
	0.05	28.93 ± 1.0321	63.83
	0.01	30.04 ± 0.5774	62.45
C	0.50	47.04 ± 0.5774	41.20
	0.05	46.98 ± 0.4539	41.27
	0.01	49.76 ± 0.2026	37.80
D	0.50	12.67 ± 0.8015	84.16
	0.05	14.83 ± 0.0238	81.46
	0.01	15.90 ± 0.3355	80.12
E	0.50	34.87 ± 0.2349	56.41
	0.05	37.15 ± 0.4560	53.56
	0.01	39.34 ± 0.9801	50.82
F	0.50	16.91 ± 0.2881	78.86
	0.05	17.45 ± 0.9880	78.18

	0.01	19.23 ± 0.8210	75.96
G	0.50	37.12 ± 0.7066	53.60
	0.05	38.91 ± 0.0444	51.36
	0.01	40.67 ± 0.9110	49.16
H	0.50	44.54 ± 0.3333	44.32
	0.05	45.12 ± 0.5774	43.60
	0.01	46.22 ± 0.5543	42.22

Table no.3: Onion root tip assay of amine substituted quinazoline derivatives.

Parameter	Conc mg/ml	No. of dividing cell observed	Total No. of cell observed	Mitotic index (%)
Control	-	91	91	100
Standard cyclophosphamide	25	43.0	110	39.0
	50	44.5	114	39.03
	100	47.8	97.5	49.02
A	25	43.21	115	37.57
	50	40.84	118	34.61
	100	37.79	123	30.72
B	25	76.21	110	69.28
	50	79.56	112	71.03
	100	80.45	99.5	80.85
C	25	72.03	111.2	64.77
	50	76.87	110.8	69.37
	100	77.14	97.4	79.19
D	25	55.23	111.02	49.74
	50	52.84	115.23	45.85
	100	53.47	99.67	53.64
E	25	74.56	111	67.17
	50	79.99	115	69.55
	100	75.91	116	65.43
F	25	42.45	110.21	38.51
	50	47.16	115.73	40.75
	100	46.33	98.08	47.23
G	25	77.46	110.73	69.99
	50	78.91	114.04	79.67
	100	79.02	99.04	79.78
H	25	71.04	112.80	62.97
	50	54.45	114.99	47.35
	100	73.81	98.45	74.97

Table No.4: Anticancer activity of amine substituted quinazoline derivatives.

Sample	Conc. (ug/ml)	Observed Viable Cell	Total cell count	% Viability	Mean ±SEM
Control	-	90	114	78.94	--
A	1000	17	110	15.45	15.45 ± 4.8
	100	21	103	20.38	20.38 ± **0.13**
	10	25	100	25	25 ± **4.75**
	1	20	99	20.20	20.20 ± **0.05**
B	1000	45	119	37.81	37.81 ± **4.83**
	100	39	108	36.11	36.11 ± 6.53
	10	48	104	46.15	46.15 ± 3.51
	1	49	97	50.51	50.51 ± 7.87
C	1000	49	113	43.36	43.36 ± 8.57
	100	55	119	46.21	46.21 ± 5.72
	10	58	103	56.31	56.31 ± 4.39
	1	60	97	61.85	61.85 ± 9.92
D	1000	18	98	18.36	18.36 ± 0.62
	100	21	101	20.79	20.79 ± 1.81
	10	20	113	17.69	17.69 ± 1.29

	1	17	89	19.10	19.10 ± 0.12
E	1000	43	112	38.39	38.39 ± 11.04
	100	48	108	44.44	44.44 ± 4.99
	10	51	96	53.12	53.12 ± 3.69
	1	55	89	61.79	61.79 ± 12.36
F	1000	21	96	21.87	21.87 ± 0.99
	100	19	94	20.21	20.21 ± 0.67
	10	18	96	18.75	18.75 ± 2.13
	1	20	88	22.72	22.72 ± 1.84
G	1000	55	103	53.39	53.39 ± 6.64
	100	51	95	53.68	53.68 ± 6.95
	10	57	93	61.29	61.29 ± 1.26
	1	61	85	71.76	71.76 ± 11.73
H	1000	51	119	42.85	42.85 ± 9.22
	100	55	105	52.38	52.38 ± 0.36
	10	59	110	53.63	53.63 ± 1.61
	1	63	106	59.43	59.43 ± 7.36
Cyclophosphamide	1000	16	114	14.03	14.03 ± 2.635
	100	18	113	15.92	15.92 ± 0.74
	10	19	110	17.27	17.27 ± 0.61
	1	21	108	19.44	19.44 ± 2.78

The compounds were screened for the anticancer activity. And they have shown moderate anticancer activity at all concentrations. Compounds A, D and F have shown excellent anticancer activity at all concentrations (1 µg /mL, 10µg/mL, 100 µg/mL, 1000 µg/mL). Standard drug used was cyclophosphamide.

Table No. 05: Anti-bacterial and Anti-fungal activity of amine substituted quinazoline derivatives.

Compd.	**Zone of inhibition at 200µg/mL (in mm.)**				
	***E*. coli**	***B*. Subtilis**	**S. aureus**	***A*. niger**	***C*. albicans**
A	**23**	**25**	**21**	**22**	**24**
B	**22**	**23**	22	18	19
C	19	**20**	19	18	16
D	**24**	**22**	**23**	**23**	**24**
E	16	14	18	15	16
F	**21**	18	**20**	**26**	**20**
G	12	14	10	8	10
H	16	14	18	12	14
Ciprofloxacin	**28**	**24**	**26**	-	-
Griseofulvin	-	-	-	**28**	**26**

Compounds **A, D** and **F,** have shown promising antibacterial and antifungal activity against *E.coli, B. subtilis, S. aureus, A.niger, and C.albicans.*

9.0. DISCUSSION

All the compounds were screened for anticancer activity by potato disc assay, onion root tip assay, Trypan blue assay and antimicrobial activity – antibacterial and antifungal activity using Cup-plate agar diffusion method, nutrient agar as media. Compounds **A**, **D**, and **F** have shown promising anticancer activity at all concentrations (1 µg /mL, 10 µg /mL, 100 µg /mL, 1000 µg /mL). However, cyclophosphamide the standard drug shows anticancer activity at 10 µg /mL. the compounds also shows excellent antimicrobial activity against *E.coli* (NCTC 10418), *B. subtilis* (ATCC 6633)**,** *S. aureus* (ATCC 29737), *A.niger* (NCIM 596) *and C.albicans* (NCIM 3102) as compared Ciprofloxacin and Griseofulvin which are the standard drugs.

10.0. CONCLUSION

The present work is the novel and bonafide work for the synthesis of 4-amine substituted quinazoline derivatives were established on the base of literature survey. Around 8 new derivatives were synthesized, with the standard chemicals. The compounds were screened for the preliminary tests, physical constant, TLC< etc. the structure of the final compound were confirmed by IR, ^{1}H-NMR Spectra and CHN analysis were carried out for prototype of compounds. This work has given out many active anticancer, antibacterial, antifungal. In near future these compounds with suitable modification can be explored better for their therapeutic activities. The vivid biological activities may consider these compounds as the lead molecule for various ailments and a lead molecule for the drug development. To find the effective

therapeutic index, the toxicity studies of these compounds can be carried out in future.

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