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Synthesis, Anticancer and Anti-Microbial Characterization of Some Novel Quinazoline Derivatives

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Abstract: ***With an objective to synthesize compounds with high anti-cancer and other anti-microbial properties, a systematically planned organic synthesis was carried out. Quinazoline has been a very significant heterocycle and also folic acid is having highly significant physiological activity. It was thought that combination of these two fragments must give resistant molecules with highly enhanced biological properties. With this ambiguous objective, the organic synthesis was carried out. The synthesized compounds were characterized by sensitive instrumental methods like Mass Spectra, ^{13}C NMR, Infra-Red Spectra, UV Spectra etc. Their structures were thus confirmed by different physicochemical methods.***

Keywords: Anticancer Activity, Antimicrobial Activity, Quinazoline derivatives and Amino Acid Derivatives

1. Introduction

Quinazoline and their derivatives constitute an important class of heterocyclic compounds. Many of them show insecticidal, analgesic, antifungal, antibacterial, anticancer, anti-inflammatory activities. Quinazoline nucleus is found in many bioactive natural products. Because of these reasons much attention is being paid for the synthesis of quinazoline derivatives. Looking at the biological significance of quinazoline nucleus it was thought to design and synthesize new quinazoline derivatives and screen them for their antibacterial activity.

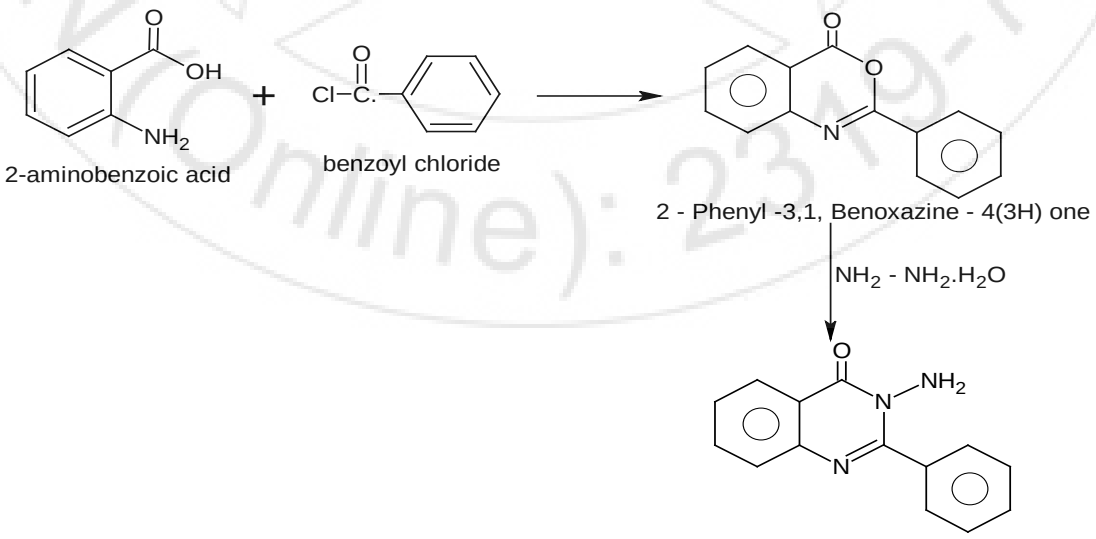
2. Materials and Method

Synthesis of quinazoline derivatives involved following steps: In the first step anthranilic acid was treated with benzoyl chloride to give 2-phenyl- 3, 1 benzoxazine – 4 [3H] one. In the next step 2-phenyl- 3, 1 benzoxazine – 4 [3H] one was allowed to react with hydrazine hydrate to give 3-amino-2-phenyl quinazoline- 4(3H)-one which was further treated with methionine and proline by the method given.

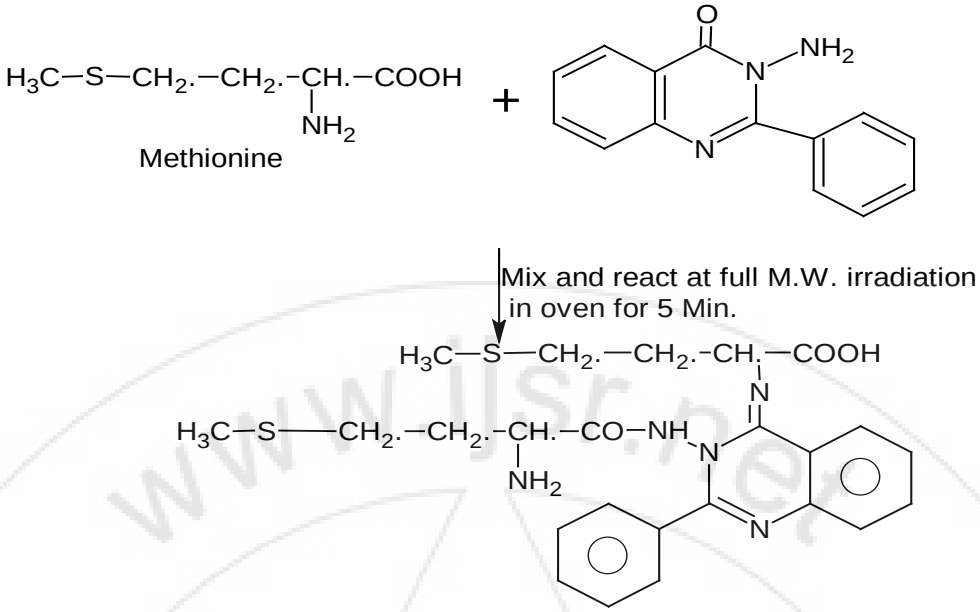
General procedure for synthesis of various 3- amino 2-phenyl quinazoline 4(3H) one and amino acid derivative.

3-amino 2-phenyl quinazoline 4(3H) one (0.0253M) in different amino acid (0.0253M) are taken and mixed to give a homogeneous mixture. This reaction mixture was taken in petri dish and it was placed in microwave oven and full microwave was set and heated for 5 min. in grilled position and after that the product was collected.

Scheme: 1

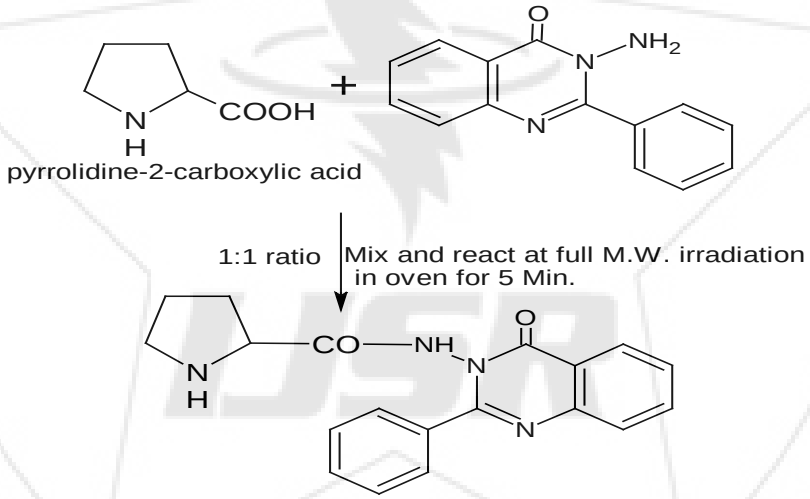


Scheme: 2



Compound - 1
3-amino 2-phenyl quinazoline 4(3H) one and Methionine derivative

Scheme: 3



Compound - 2
3-amino 2-phenyl quinazoline 4(3H) one and Proline derivative

3. Spectra Characterization

Compound-1: 3-amino 2-phenyl quinazoline 4(3H) one and Methionine derivative

Elemental Analysis: %C %H %N %S

Found 59.05 5.91 13.96 8.78

Calculated 57.51 5.85 14.02 12.82

Infrared spectral Features (cm^{-1}): cm^{-1} Assignment
1637 C=N Stretching
3213,3307 -$CONH_2$, -NH- Stretching
1563, 1588, 1611 -$CONH_2$, -NH- Bending
1661 C=O Stretching
2915 Aromatic C-H Stretching
1588, 1611 C=C Stretching
1448, 1370 Alkenes –CH_3 bending
1472 Alkenes –CH_2- bending
2577 S-H, -S- Stretching

^{13}C Spectral Features (ppm): (ppm) Assignment
38.55, 39.27, 39.48, 39.69, 39.90, 40.10 R_2-CH_2, R_3-CH, R_4-C
78.50, 78.83, 79.16 C-N
146.67, 155.50 R-CO-NH
125.95, 126.50, 126.88 127.30, 127.37, 129.52,
134.03, 134.76 Benzene
161.11, 167.80 =C=O

Mass Spectral Features: (ppm) Assignment
499 Molecular peak is observable
500 (M+1) Molecular peak is observable
501 (M+2) molecular peak is observable
483 Base peak is observable for (M - CH_2)

278 Peak is observable for (M – $C_8H_{17}N_2S_2O$)
238 Peak is observable for (M – $C_{10}H_{17}N_2S_2O_2$)
260 Peak is observable for (M - $C_8H_{17}N_2S_2O.H_2O$)
150 Peak is observable for Methionine (M+1)

UV Spectral Features: λ_{max} Assignment
289 n→π^* Substituent with lone pair R-band
248 π→π^* Substituent Delocalized by Aryl K-band
215,221 π→π^* Allowed

Compound – 2: 3-amino 2-phenyl quinazoline 4(3H) one and Proline derivative
Elemental Analysis :
%C %H %N
Found 63.24 5.62 15.23
Calculated 66.82 6.08 16.24
Infrared spectral Features (cm^{-1}) :
cm^{-1} Assignment
1635 C=N Stretching
3214,3307, 3358, 3442, 3507 -$CONH_2$, -NH- Stretching
1563, 1574, 1590, 1611 -$CONH_2$, -NH- Bending
1661 C=O Stretching
3035, 3061 Aromatic C-H Stretching
1590, 1611 C=C Stretching
1448, 1371 Alkenes –CH_3 bending
1471 Alkenes –CH_2- bending
^{13}C Spectral Features (ppm) :
(ppm) Assignment
22.83, 2379, 27.16, 28.90 R-CH_3
38.89,39.31,39.73,40.14, 44.45, 45.15, 59.73,60.49 R_2-CH_2, R_3-CH, R_4-C
78.48,78.81, 79.14 C-N
146.67,155.44 R-CO-NH
125.94, 126.44, 127.27,128.49,129.34, 131.15, 131.35, 133.97, 134.75 Benzene
161.08, 164.23, 165.87 =C=O
Mass Spectral Features :
(ppm) Assignment
335 (M+1) Molecular peak is observable
238 Peak is observable for (M – C_5H_6NO) Quinazoline peak
116 Peak is observable for Proline (M+1)
UV Spectral Features :
λ_{max} Assignment
290 n→π^* Substituent with lone pair R-band
252 π→π^* Substituent Delocalized by Aryl K-band
206,220 π→π^* Allowed

Table 1: Various 3-amino 2-phenyl quinazoline (3H) one derivative

Sr. No.	Compound Name	M.P	Solubility	Nitrogen Rule Obeyed	Rules of 13		Compound Formula	Base formula	Unsaturation Index U
					n	r			
1	Comp. 1	246	DMSO	yes	28	4	$C_{24}H_{29}N_5O_3S_2$	$C_{38}H_{43}$	23
2	Comp. 2	176	DMSO	yes	25	9	$C_{19}H_{18}N_4O_2$	$C_{25}H_{34}$	13

4. Antimicrobial Activity

Antibacterial activity was performed by cup plate method by measuring zone of inhibition. All the test compounds were screened for antibacterial activity against bacterial strains *Staphylococcus aureus, Bacillus sp., Salmonella typhi* and *Escherichia coli* (ESS 2231) at a concentration of 200, 300, 400 µg/ml. Ampicillin was used as standard drug at a concentration of 200, 300, 400 µg/ml, Nutrient agar was used as culture medium & DMF was used as solvent control.

The plates were inoculated within minutes of the preparation of suspension, so that the density does not change. A sterile cotton swab over was dipped into the suspension and the medium was inoculated by even streaking of the swab over the entire surface of the plate in three directions. After the inoculums had dried, cups of diameter 6mm were made in the agar plate with a sterile cork borer. The drugs solutions were added to these cups with a micropipette and the plates were then incubated at 37 0C for 24 hours. The zone of inhibition was measured using mm scale.

The fungicidal activity of all the compounds was studied at 1000ppm concentration. Invitro plant pathogenic organisms used were *Aspergillus* SP, Yeast, etc with standard antifungal, antibiotic fluconazol. The antifungal activity of all the compounds was measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium such a PDA medium contained potato 200gm, dextrose 20gm, agar 20gm, and water 1 liter. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120°C for 15 min. and at 15 atm pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below.

Percentage of Inhibition =100(X-Y)/X
Where, X = Area of colony in control plate Y= Area of colony in test plate

Table 2: Antibacterial Activity of Compounds

Compound Name	Zone of Inhibition (in mm)											
	Gram Positive			Gram Negative								
	Bacillus Sp.			Staphylococcus Aureus			E. Coli			Salmonella Typhi		
	200 µg/ml	300 µg/ml	400 µg/ml	200 µg/ml	300 µg/ml	400 µg/ml	200 µg/ml	300 µg/ml	400 µg/ml	200 µg/ml	300 µg/ml	400 µg/ml
Comp-1	18	23	22	25	28	30	22	25	28	15	19	24
Comp-2	17	23	28	--	--	18	--	--	17	--	18	24

Table 3: Antifungal Activity of Compounds

Compound Name	Zone of Inhibition (in mm)					
	Aspergillus Sp.			Yeast		
	200 µg/ml	300 µg/ml	400 µg/ml	200 µg/ml	300 µg/ml	400 µg/ml
Compound- 1	13	18	23	18	22	25
Compound- 2	--	18	22	24	27	30

5. Anti Cancer Experimental Setup

5.1 Cell Lines and Culture Medium

MDA-MB-468 and HCT-15 cultures used in these experiments were derived from National Centre for Cell Science (NCCS), Pune. Stock cells of these cell lines were cultured in DMEM, supplemented with 10% FBS (fetal bovine serum). Along with media cells were also supplemented with 5% HBSS, penicillin, streptomycin and Amphotericin – B, in a humidified atmosphere of 5 % CO_2 at 37°C until confluence reached. The cells were dissociated with 0.2% trypsin, 0.02% EDTA in phosphate buffer saline solution. The stock cultures were grown initially in 25 cm^2 tissue culture flasks, than in 75 cm^2 and finally in 150 cm^2 tissue culture flask and all cytotoxicity experiments were carried out in 96 microtitre well- plates. 2×10^4 cells/well was added in to each well of 96 well-plates.

Table 4: Results of MDA-MB-468 cell line

Conc. µM/ml	Log con.	% Cell Inhibition		
		Compound - 1	Compound - 2	Std. Doxorubicin
0.01	-2.29	-2.20	-5.06	-40.87
0.02	-1.82	-1.43	-7.01	-32.81
0.05	-1.34	-1.72	-7.01	-29.69
0.14	-0.86	-0.34	0.26	-17.63
0.41	-0.39	10.88	0.95	-14.34
1.23	0.09	13.17	0.84	-12.55
3.70	0.57	22.68	2.65	11.25
11.11	1.05	28.09	6.97	48.35
33.33	1.52	39.14	10.22	71.32
100.00	2.00	57.18	35.32	86.69
IC_{50} (µM/ml)		31.96	>100	6.802
R^2		0.9184	0.9593	0.9833

6. Result and Discussions

Antibacterial activity of compound 1 is good at lower as well as higher concentrations against E. Coli, S. aureous and bacillus sp. whereas against S. typhi, A. sp. and yeast is moderate to low in comparison with standard antibiotic. Compound 2 shows good activity against B. sp. and yeast. For other organisms, it shows less activity compared to the standard antibiotic.

Potent compounds with good cytotoxicity but less than std. drug.>M15. While no cytotoxicity effect by M17 compounds because of Ic50 values is more than 100. Therefore it would be better to go for further study of the non-toxic compound series after checking of its toxicity with normal cell line and then one can go for establishing mechanism based study of that series of compounds by using Tunnel assay, Flow cytometry, DNA fragmentation assay Or CASPACASE assay

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