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Synthesis and Evaluation of Some New 4, 6-Disubstituted Quinazoline Derivatives for Antimicrobial and Antifungal Activities

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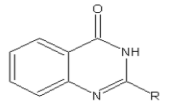
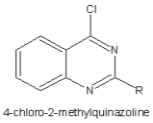
Abstract

Promising antimicrobial and antifungal activities have been reported in many substituted quinazoline derivatives. Earlier, Quinazoline-4-ones has been a subject of extensive pharmacological evaluation, as well as, toxicological studies for antimicrobial and antifungal activities. Its 4-chloro analog has recently revealed much superior activity to it.



2-methylquinazolin-4(3*H*)-one



4-chloro-2-methylquinazoline

Scientific research and clinical studies have already documented the value of Quinazoline-4-ones in treating various microbial diseases. With this rationale, the synthesis and biological evaluation of new 4, 6-disubstituted quinazoline derivatives was undertaken through various synthetic routes.

The newly synthesized derivatives have been characterized through chromatography & physical constant determination. The newly synthesized derivatives were evaluated for their antimicrobial activity against *E.coli* & *S. aureus* & for antifungal activities against *candida albicans* and found promising antimicrobial and antifungal activities.

Keywords: Quinazoline, Synthesis, Chlorination, Antimicrobial, Antifungal

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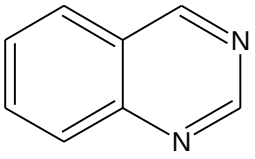
INTRODUCTION

Quinazoline (1, 3- diazanaphthalene) was prepared by Gabriel in 1903 although the first derivative was synthesized by Griess. The name was proposed by Widdege, other names such as phenmiazine, benzo-1, 3-diazine and 5; 6-benzopyrimidine has occasionally been used. The numbering suggested by Paal and Busch is still in use[1].



Quinazoline

The presence of a fused benzene ring alters the properties of the pyrimidine ring considerably. The two nitrogen atoms are not equivalent and the marked polarization of the 3, 4- double bond is reflected in the reactions of quinazoline[9]. The properties of substituted quinazolines largely depend on:

(a) The nature of the substituent.

(b) Whether they are in the pyrimidine ring or in the benzene ring,

(c) And whether or not complete conjugation is present in the pyrimidine ring.

The reduction of quinazoline was complicated by covalent hydration in acidic solution, because the hydrated species were not easily reduced. The anhydrous species in alkaline medium were reduced stepwise to dihydro and then to tetrahydroquinazoline and the dihydro radical intermediate was capable of dimerization. The protonation rates of N-heterocyclic in aqueous solution could be determined by polarographic technique. The rates for quinazoline and pyrimidine were too fast for measurement which was consistent with predictions from quantum chemical calculation[2].

Quinazoline shows broad variety of biological activity profiles, such as analgesic, anti-inflammatory, antibacterial, diuretic, antihypertensive, antimalarial, sedative, hypoglycemic, antibiotic, antitumor etc. These examples clearly demonstrate the potential of quinazoline derivatives as a source of useful pharmacophore for new drug evolution.

As our interest in search for biological heterocycles, we sought an unexplored, synthetically accessible heterocyclic template (quinazoline) capable of bearing some potential pharmacophore to elicit and enhance inherent biological activity. In addition, quinazoline derivatives also have a therapeutic benefit as an anti-invasive agent with potential for activity in early and advanced solid tumors, metastatic bone disease and leukemia. Some of the known quinazoline derivatives exhibited remarkable anticancer activity. However search is continuously on to identify more potent lead molecules as these molecules are developing resistance over a period[10].

Based on the importance of these molecules, our attention was attracted towards synthesis of novel quinazoline derivatives in order to find more potent molecules. Among a wide variety of nitrogen heterocyclic that has been explored for developing pharmaceutically important molecules, the quinazoline have played an important role in the medicinal chemistry and subsequently emerged as a pharmacophore. There has been an increasing interest in the chemistry of 4(3H)-quinazoline because of their biological significance[3].

The rapid rise in bacterial resistance to the traditional antibiotics such as penicillin and tetracycline has encouraged as a search for new classes of compounds with novel modes of antibacterial activity, the quinazoline nucleus have emerged as an area of immense interest because of their broad spectrum of in *vitro* and there in *vivo* chemotherapeutic efficiency.

MATERIALS AND METHODS:

Anthranillic acid (2-amino benzoic acid) was reacted with acetyl chloride in dry pyridine at 0-5^{o}C for 4 hrs and obtained benz-oxazinone in high yields. Benzoxazinone is further treated with aq. Ammonia at room for and results in respective amide derivative. This amide derivative on refluxing with aq. sodium hydroxide gave cyclised product quinazoline-4-one. It is further chlorinated using PCl_5 and obtained 4-chloroquinazoline. In order to see the role of substituent on rate of reaction, yield of products and subsequently on activity, anthranilic acid was substituted with bromine/iodine in fifth position and the sequence of reactions is carried out to obtain the respective products are independent of substituent used[4]. The sequences of reactions are drawn in scheme and yield of products are tabulated in Table.1.

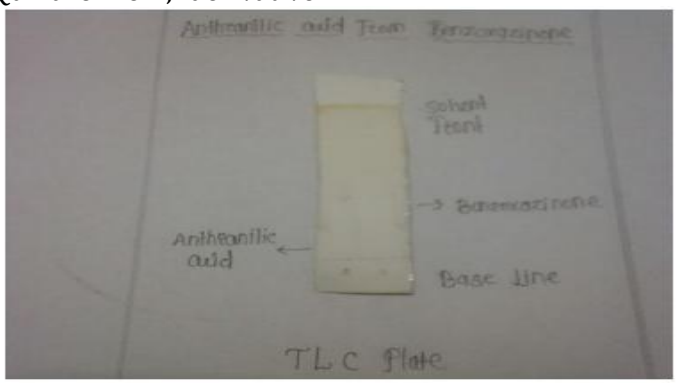
Anthranilic acid from phthalimide[7]:

3gm of NaoH in 26.4 ml of Water in conical flask at cool and 2.6 g of bromine in one portion and shake and cool again finely prepare powder of pthlamide in one portion to cool Hypobromide solution. Remove the from the cooling bath lvigrously until clear yellow solution obtainand add NaoH solution Rapidly then cool it solution add conc. HCl with slowly stirring until

solution with Neutral ppt gradual addition of GAA and Recrystalise with ethanol.

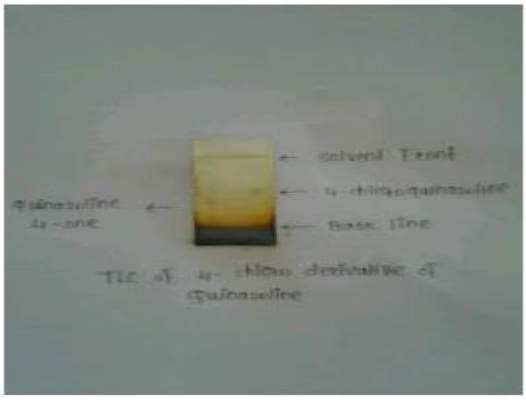
Benzoxazinone from Benzidine[7]:

Take 0.54g of benzoxazionone and add Amide containing drug o.54gm of Acetamide attach it reflux containing to condenser and reflux for 6hrs with gradually addition of glacial acetic acid and the progress of reaction was monitored and after complection of reaction content poured on to the crushed ice to from solid mass which was collected and Recrystaliseand in presence og NaoH to obtain of Quinazoline-4,1derivative.

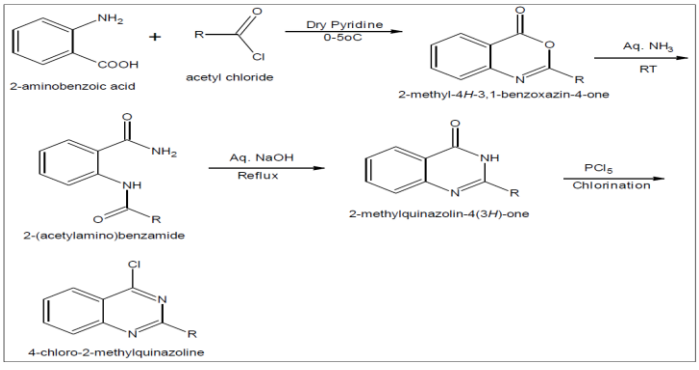


Chlorination of quinazoline-4-one by using phosphrous pentachloride[7]:

A solution of 4-oxoquinazoline derivative (3.73g) and 1g of phosphorous penta chloride(Pcl5)was heated in 2hrs then reaction micture was cooled and diluted with ice water and ppt was coolected Recrystalise from chloroform to obtain 4- Chloroquinazoline Derivative.



Scheme



RESULTS & DISCUSSION:

Quinazoline derivatives being considered as potent antimicrobial agents. There are several new Quinazoline derivative QZ-1 to QZ-4 were synthesized and screened for antimicrobial activity. It was found that, all synthesized compound show good activity against gram +ve and –ve activity and antifungal activity against candida albicans. The study shows activity relationship between the antimicrobial activity certain structural modificatin of these new quinazoline derivative[11].

Melting points were recorded by open capillary method (Thiel's tube method). All reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F 254 (mesh); spots were visualized under UV light. Meck silica gel (100-200 mesh) was used for chromatography[6].

Compound no.	X	M.P. (˚c)	Yield (%)
QZ-1	CH_3	92˚ C	67.3
QZ-2	HBr	97˚C	70.2
QZ-3	CH_3I	112˚C	60.2
QZ-4	OCH_3	98˚C	71.2

Table 1: Synthesis of 4, 6 – disubstituted quinazoline derivatives

Biological activity:

1. Antimicrobial Activity:

a) Inhibition of Escherichia coli:

All compound shows minimum inhibitory concentration of E. coli ranges between 50 to 100 ml. The compound of 6-Bromo-2-phenylquinazoline4[3H]-one[QZ-2] showed best activity among all Quinazoline derivative but showed less activity than that of standard drug and screened for antimicrobial activity promising compound which showed activity have been identified[5].

b) Inhibition of Staphylococcus aureus:

Compound QZ-2 showed inhibitory effect at concentration 50µg/ml (minimum MIC) and compound QZ-1, QZ-3 and QZ-4 showed inhibitory effect at concentration 100µg/ml respectively. On the basis of the antimicrobial activity, it was found that the compound QZ-2 showed good antimicrobial activity in comparison to all other synthesized compounds.

All synthesized compounds showed antimicrobial activity against gram positive and gram negative bacteria12.

The study showed the structural activity relationship between the antimicrobial activity and certain structural modifications of these new quinazoline derivatives. The compound QZ-2 was found to be most effective against *Escherichia coli* and *Staphylococcus aureus* at concentration of 50 and 100µg/ml respectively. The compounds QZ-1, QZ -3 and QZ-4 were found to be least effective against *E.coli* and *Staphylococcus aureus*[13]. In general the order of an antimicrobial activity of quinazolines derivatives is as follows -:

QZ-2> QZ-1> QZ-3>QZ-4

These variations in the antimicrobial activity occurred due to some structural changes in the synthesized compounds. An introduction of substituent at C-6 position in quinazoline nucleus was found to be active against all microorganisms[5].

1. Antifungal Activity:

a) Inhibition of *Candida albicans:*

Sr. No.	Compound	Zone of Inhibition (mm)	
		50	100
1.	Qz-1	14	12
2.	Qz-2	17	19
3.	Qz-3	14	13
4.	Qz-4	10	12
Standard	Ciprofloxacin	28	30

Table 2: Antimicrobial activity of 4, 6 – disubstituted quinazoline derivatives

CONCLUSION:

A series of novel substituted quinazoline derivatives have been synthesized through a facile strategy and screened for their antimicrobial and antifungal activities and found promising both the activities.

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