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SYNTHESIS AND PHARMACOLOGICAL EVALUATION AS ANTIMICROBIAL AGENT OF SOME NOVEL QUINAZOLINONE DERIVATIVES

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ABSTRACT
A series of Quinazolinone derivatives (DK-1, DK-2, DK-3, DK-4, DK-5, DK-6 & DK-7) have been synthesized by treating 2-chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl) acetamide with different substituted phenols in presence of anhydrous potassium carbonate and catalytic amount of potassium iodide in dry acetone. The structures of the compounds were characterized on the basis of their melting Point, TLC, IR and ^{1}H-NMR data. All the synthesized compounds were evaluated for anti-microbial (antibacterial and antifungal) activities.

KEYWORDS: Quinazolinone, anti-microbial (antibacterial and antifungal) activities.

1. INTRODUCTION

Medicinal chemistry remains a challenging science which provides profound satisfaction to its practitioner. It intrigues those of us who like to solve problems posed by nature. It verges increasingly on biochemistry and on all the physical, genetic and chemical riddles in animal physiology which bear on medicine. Medicinal chemists have a chance to participate in the fundamentals of prevention, therapy and understanding of diseases and thereby to contribute to healthier and happier life.[1]

Medicinal chemistry as an important science started less than 100yrs ago. The active principles of plants mostly alkaloids were isolated and were the starting point for synthesis.

In medicinal chemistry, the chemist attempts to design and synthesize a medicine or a pharmaceutical agent which will benefit humanity. Such a compound could also be called a “drug”, but this is a word which many scientists dislike since society views the term with suspicion.[2]

Success in drug discovery is dependent on the ability to identify novel, patentable compounds known colloquially as New Chemical Entities (NCEs) that have the potential to treat a disease in a safe and efficacious manner. While enabling technology platforms like genomics and combinatorial chemistry contribute significantly to this process, a proprietary NCE position is absolutely essential to ensure marketing exclusively and to justify the investment in the R & D process, making medicinal chemistry a core element of the drug discovery process. Drug discovery can be divided into four distinct steps: target identification and selection, target optimization, lead identification, and lead optimization.[3]

The research activity in synthetic organic chemistry during the last few years is more focused on the development of rapid synthetic protocols for building proven biologically active complex molecular scaffolds and also on preparing novel molecules for evaluating their potential to be used as drugs, pharmaceuticals, agrochemicals and specialty chemicals. The potency of any organic molecule towards its biological activity is measured in terms of lower dosage, non-toxic nature and effective binding to specific receptor site to control the replication of harmful microorganism for the inhibition of disease. Apart from the size and geometry of the molecule, the presence of a specified functional group in strategic position acting as a pharmacophore is essential for possessing activity. Enzyme receptor sites being considered as Lewis acidic sites, hetero atoms or ligands which can donate electrons can binds to acidic sites. Thus, several derivatives of coumarines, quinolines, 1,2,4-triazoles, 1,3,4-oxadiazoles and hydrazones along with amines substituted with functional groups containing hetero atoms are found to show a wide range of biological activities.

DRUG DESIGN:[4] ‘Drug design’ or ‘tailor-made compound’ aims at developing a drug with high degree of chemotherapeutic index and specific action.

Drug design seeks to explain.

- Effects of biological compound on the basis of molecular interaction in terms of molecular structures or precisely the physico-chemical properties of the molecules involved.
- Various processes by which the drug usually produce their pharmacological effects.
- How the drug specifically react with the protoplasm to elicit a particular pharmacological response.
- How the drugs usually get modified or detoxicated, metabolized or eliminated by the organism.
- Probable relationship between biological activities with chemical structure.

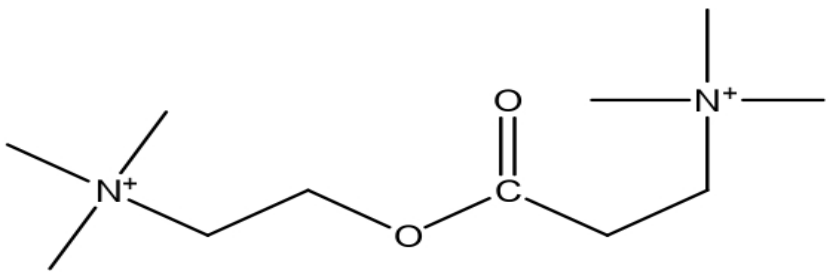
METHODS OF DRUG DESIGN

❖ **DRUG DESIGN THROUGH CONJUNCTION METHOD**

In this method a new drug molecule is developed from a biologically active prototype. This is known as the systemic formulation of analogues of a prototype agent, to word structurally complex produces, which may be viewed as structures embodying in a general or specific way. In this type of the drug design, the main principle involved is the principle of mixed moieties.

A drug molecule is essentially made up with two or more pharmacophoric moieties embedded in to a single molecule or conjunction of two or more different type's pharmacophoric moieties within single molecules.

EAMPLE: Hexamathonium**,** promptly suggests the following design, thus embodying the ganglionic moiety and the muscarinic moiety in to a single molecule by using the structure of acetyl choline.



Hexamathonium

Now in this we synthesis a different derivatives of some novel Quinazolinone. In which after synthesis their pharmacological evaluation as antimicrobial agent are used.

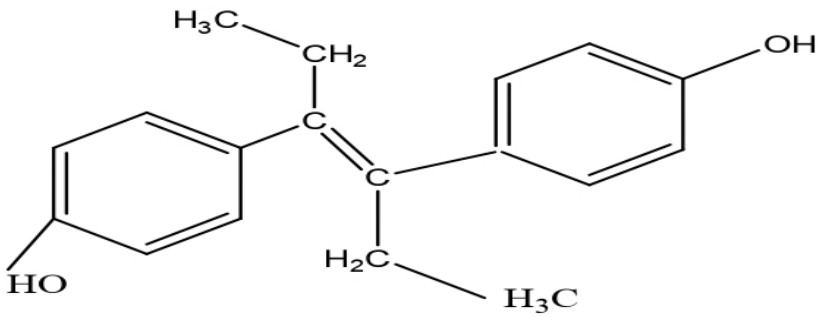
DRUG DESIGN THROUGH DISJUNCTION METHOD

Disjunction comes in where there is the systematic formulation of analogues of a prototype agent, in general, to ward structurally simpler products, as partial or quasi-replicas of the prototype agent.

De-conjunction method usually employed in three different manners, namely.

- Unjoining of certain bond
- Substitution of aromatic cyclic system for saturated bond
- Diminution of the size of the hydrocarbon portion of the parent molecule

Example: The estrogenic activity of oestradiol via drug design through disjunction ultimately rewarded in the crowning success of the synthesis and evaluation of trans-diethyl- Stilbestrol.



trans-Diethylstilbesterul

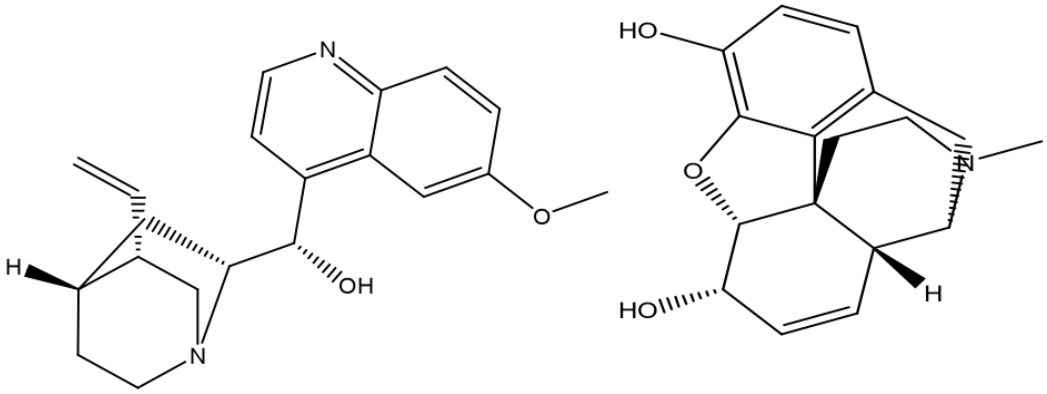
LEAD COMPOUND[5]

A Compound which shows the desired pharmaceutical activity the level of activity may not very great and there may be undesirable side effects, but the lead compound provides a start for the drug development process.

Example; Medicines are either obtained directly from a natural source or were developed from a lead compound originally obtained from a natural source.

Artemisinin is one such example containing as it does an extremely unstable looking trioxide ring. Example: Plant and trees have always been a rich source of lead compound.

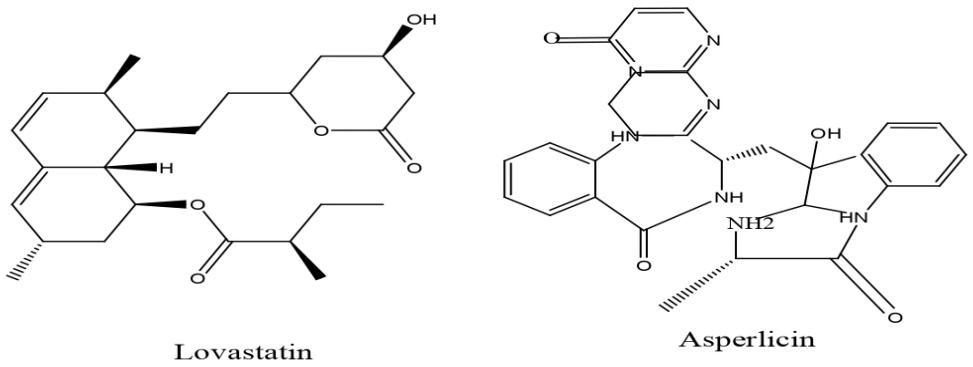
Like: Morphine, cocaine, Cardiac-glycoside, Quinine.



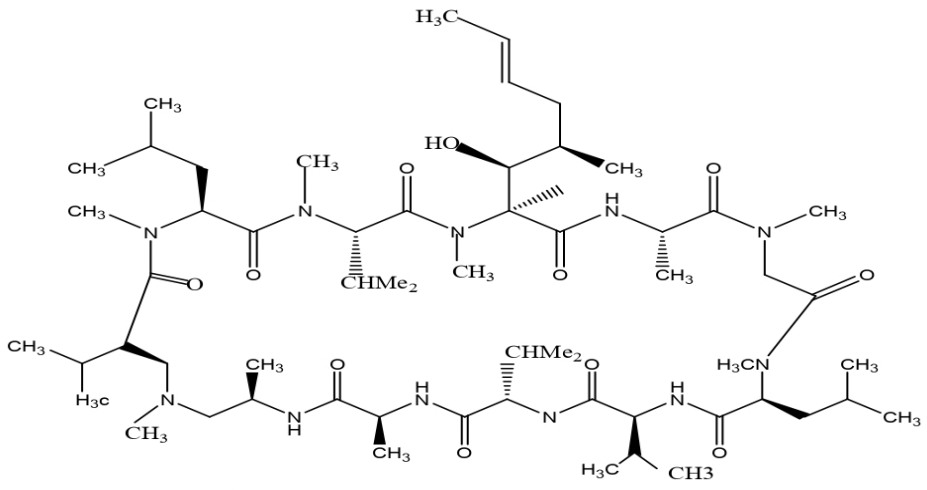
QUININE MORPHINE

Example; Microorganisms (bacteria and fungi) also provided rich picking for drugs and lead Compound.

1. Asperlicin isolated from Aspergillus alliaceus.
2. Lovastatin isolatedfrom Aspergillus terreus.
3. cyclosporinisolatedfrom Aspergillus alliaceus.



Lovastatin Asperlicin



Cyclosporin

Antimicrobial Agents[6]

An antimicrobial is a substance that kills or inhibits the growth of microbes such as bacteria, fungi, or viruses. it is a general term that refers to a group of drugs that includes antibiotics, anti-fungal, anti- protozoals and antiviral and used to treat a microbial infection. Antimicrobial drugs either kill microbes (microbicidal) or prevent the growth of microbes (microbistatic).

Antimicrobial agents are.

- Antibacterial
- Antifungal

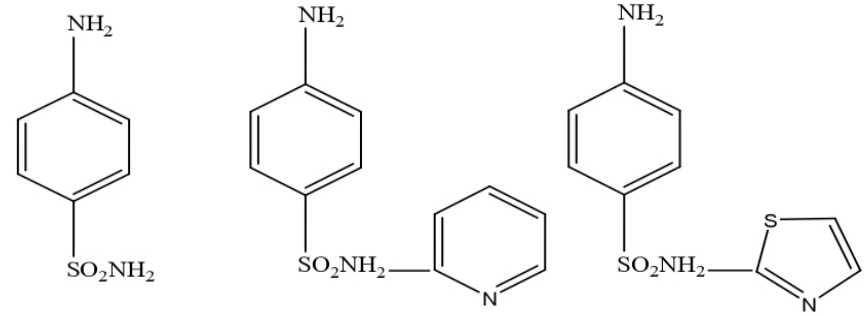
Antibacterial: Antibacterial antibiotics normally act by either making the plasma membrane of bacteria more permeable to essential ions and other small molecules by ionophoricaction or by inhibiting cell wall synthesis. Those compounds that act on the plasma membrane also have the ability to penetrate the cell wall structure. In both cases, the net result is loss in the integrity of the bacterial cell envelope, which leads to irreversible cell damage and death.

The activity of the penicillins and cephalosporins is believed to be due to the B-Lactum ring. Bacterial resistance to these drugs is thought to be mainly due to inactivation of the drug by hydrolysis of the B- Lactum ring by the B-lactamases produced by the bacteria. Both Gram-positive and Gram-negative bacteria produce B-lactamases. In the former case, the enzyme is liberated into the medium surrounding the bacteria, which results in the hydrolysis of the B -Lactum ring before the drug reaches the bacteria.

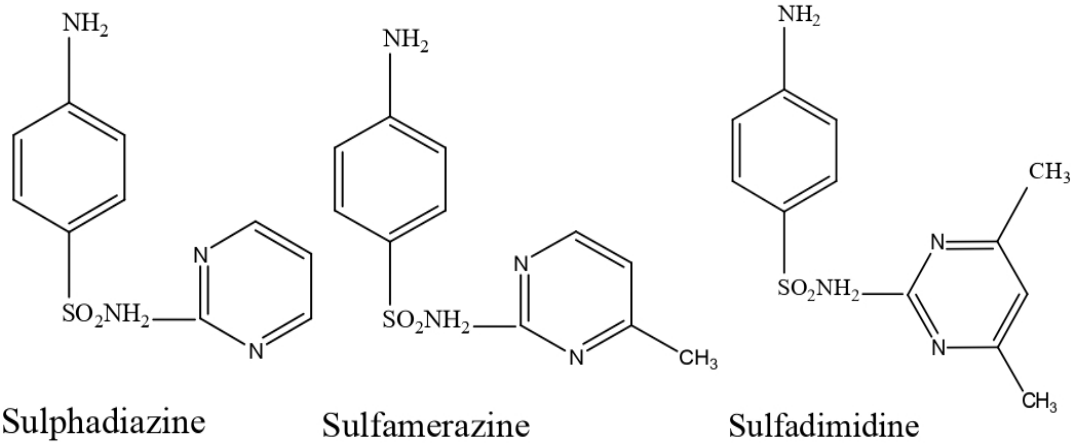
Classification[7]

Antibacterial agents are classified in 3 groups.

- **Sulfonamides:** Sulfanilamide, Sulfathiazole, Sulfapyridine, Sulfadiazine, Sulfadimidine, Sulfamerazine.

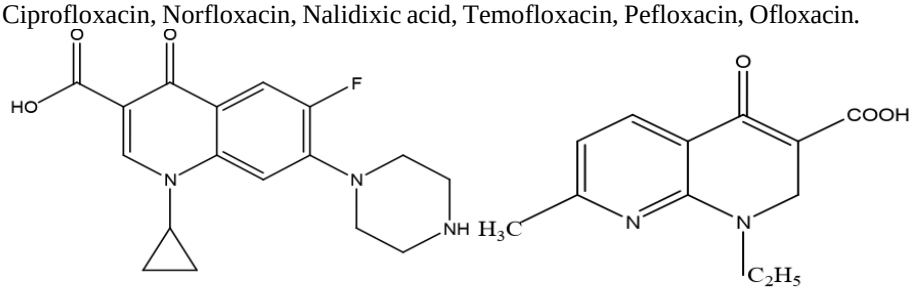


Sulfanilamide Sulfapyridine Sulphathiazole



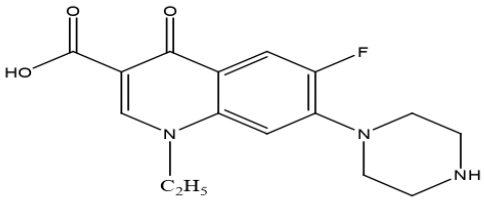
Sulphadiazine Sulfamerazine Sulfadimidine

- **Quinolones:** Ciprofloxacin, Norfloxacin, Nalidixic acid, Temofloxacin, Pefloxacin, Ofloxacin.

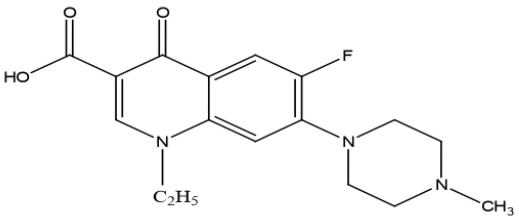


Ciprofloxacin

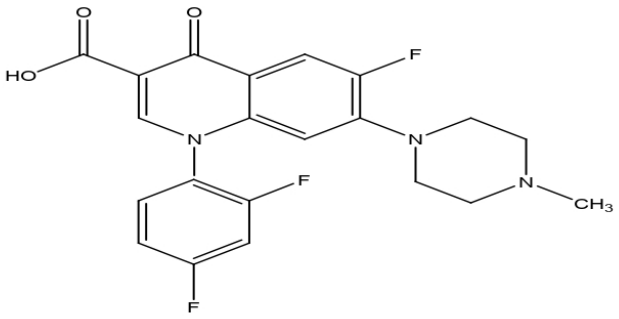
Nalidixic acid



Norfloxacin



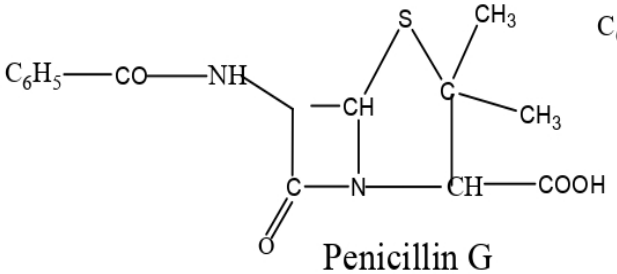
Pefloxacin



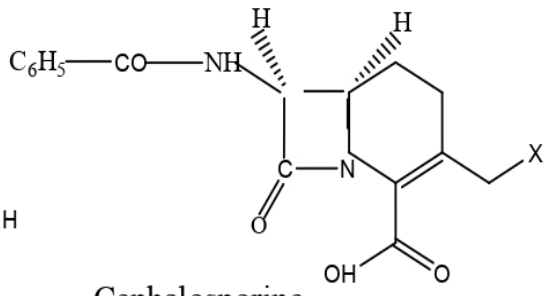
Temafloxacin

- **Antibiotic:** Antibiotic will be discussed explicitly under the 4 main heads:

➢ B.lactom antibiotics. Penicillins, Cephalosporin

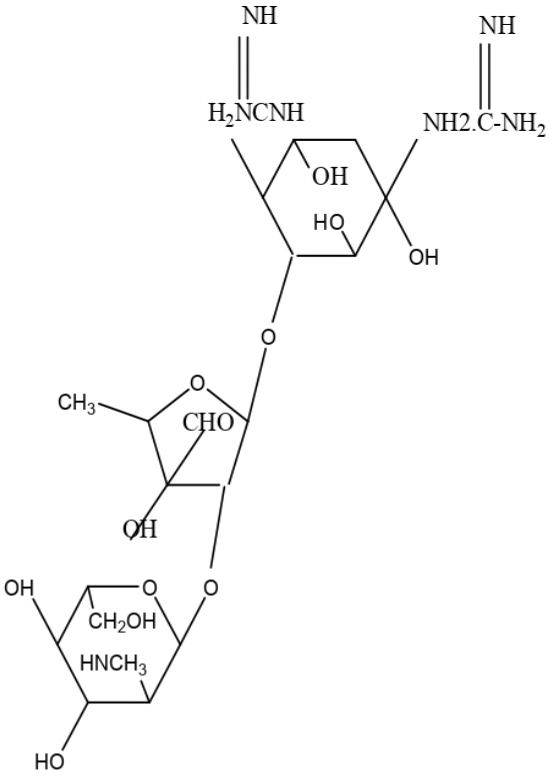


Penicillin G

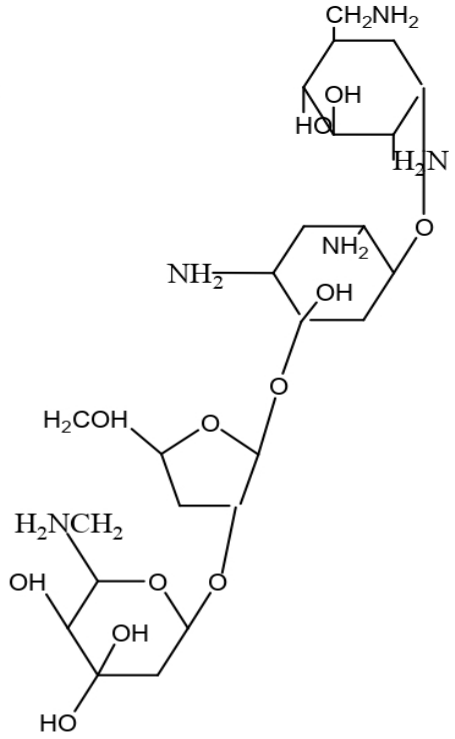


Cephalosporine

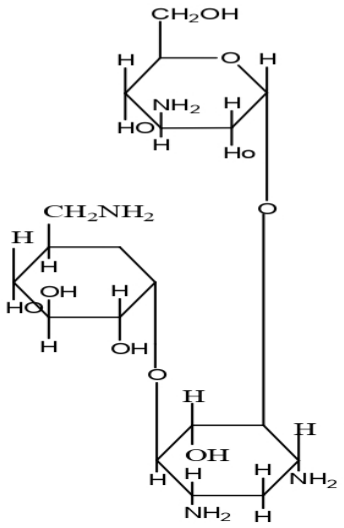
- Amino-glycoside antibiotics. Streptomycin, Neomycin, Kanamycin



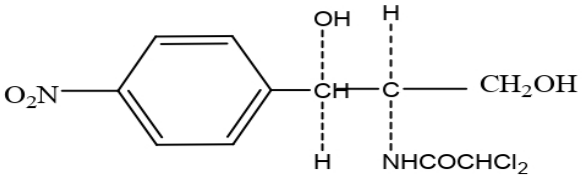
Streptomycin



Neomycin

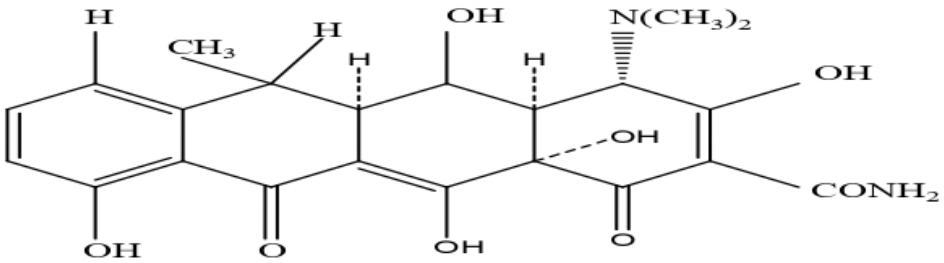


Kanamycin

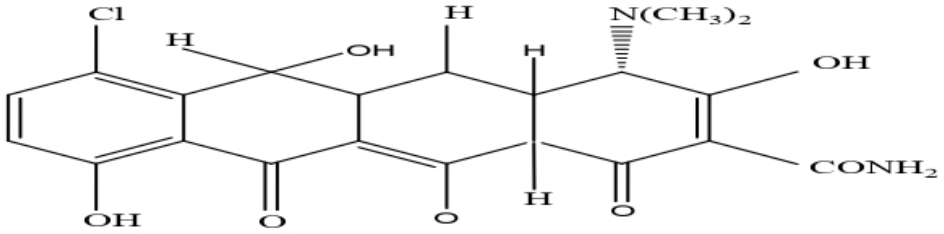


Chloramphenicol

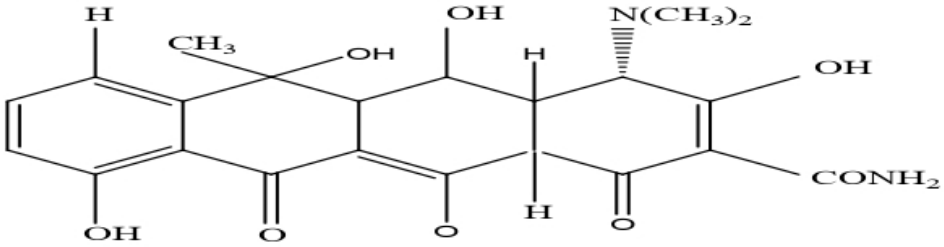
- Tetra-cyclines: Doxycyclin, Methacycline, Demeclocycline, Oxytetracycine



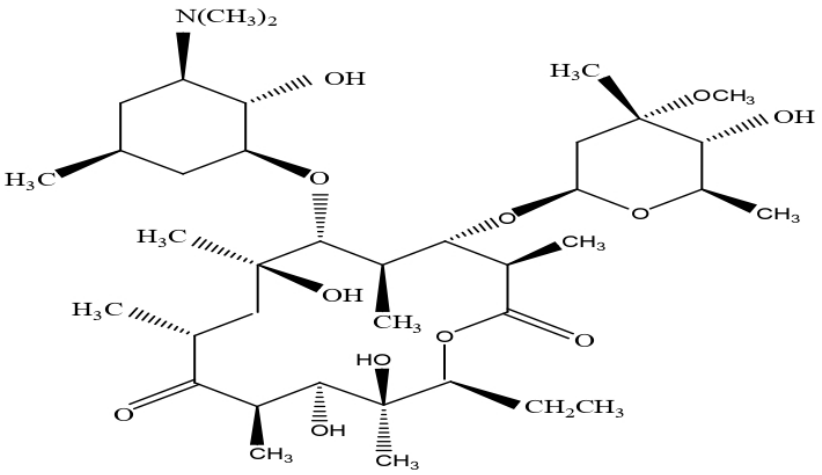
Doxycycline



Demeclocycline

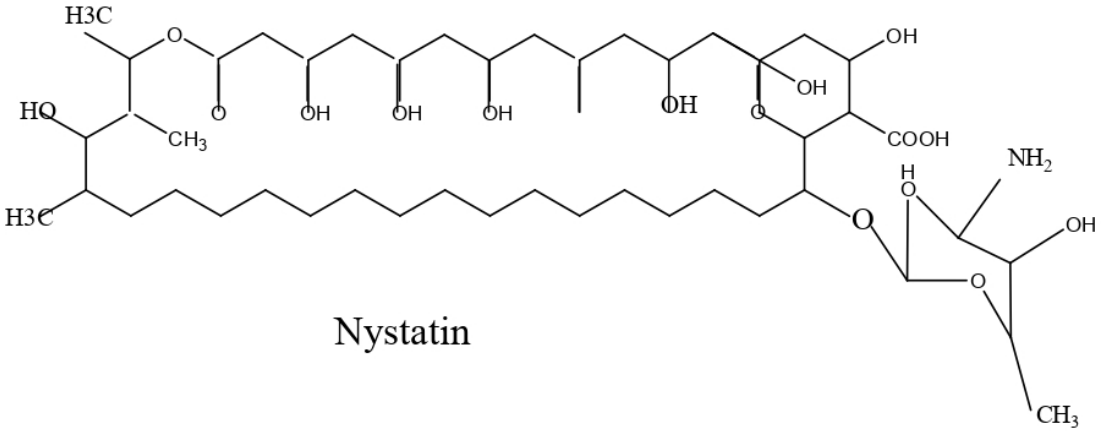


Macrolide antibiotics: **Erythromycin**



Erythromycin

- **Polyene antibiotics: Nystatin, Amphotericin-B**



Nystatin

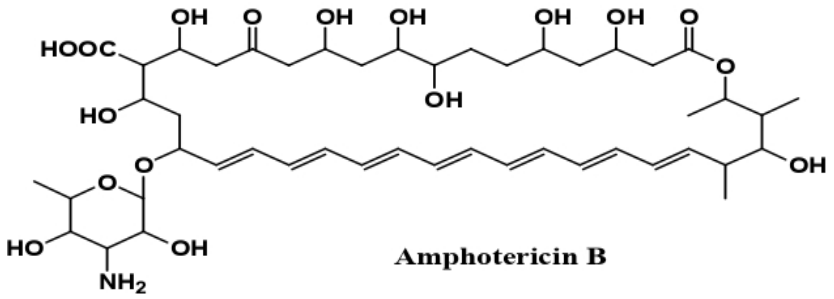
Antifungal[8]

Fungal skin infections are caused by 'dermatophytes', which are parasitic fungi affecting the skin, hair, or nails. There are three groups of dermatophytes, called Trichophyton (affects skin, hair and nails), Microsporum (a type of fungus that causes ringworm epidemics in children) and Epidermophyton (A fungal which grows on the outer layer of the skin and is the cause of tinea). Dermatophytes also produce what is widely known as 'Ringworm', in which the fungi limit themselves to dead Keratin, a protein found on the skin. Fungi that have developed to live on animals can also infect us, and will usually cause much more inflammation and redness because our immune system sees them as a foreign invasion and goes into attack.

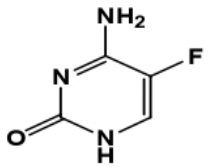
The development of antifungal agents has lagged behind that of antibacterial agents. This is a predictable consequence of the cellular structure of the organisms involved. Bacteria are prokaryotic and hence offer numerous structural and metabolic targets that differ from those of the human host. Fungi, in contrast, are eukaryotes, and consequently most agents toxic to fungi are also toxic to the host. This difficulty complicates experiments designed to evaluate the *in vitro* or *in vivo* properties of a potential antifungal agent.

Polyene Antifungal Drugs

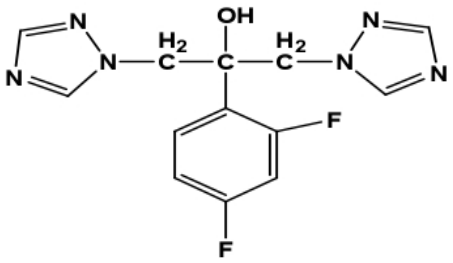
The polyene compounds are so named because of the alternating conjugated double bonds that constitute a part of their macrolide ring structure. The polyene antibiotics are all products of *Streptomyces* species. These drugs interact with sterols in cell membranes (ergosterol in fungal cells; cholesterol in human cells) to form channels through the membrane, causing the cells to become leaky. The polyene antifungal agents include nystatin, amphotericin B, and pimaricin.



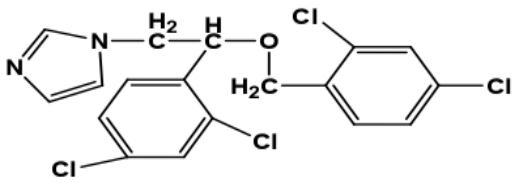
Amphotericin B



Flucytocin



Fluconzole



Miconazole

Figure 1: Structures of some common antifungal agents.

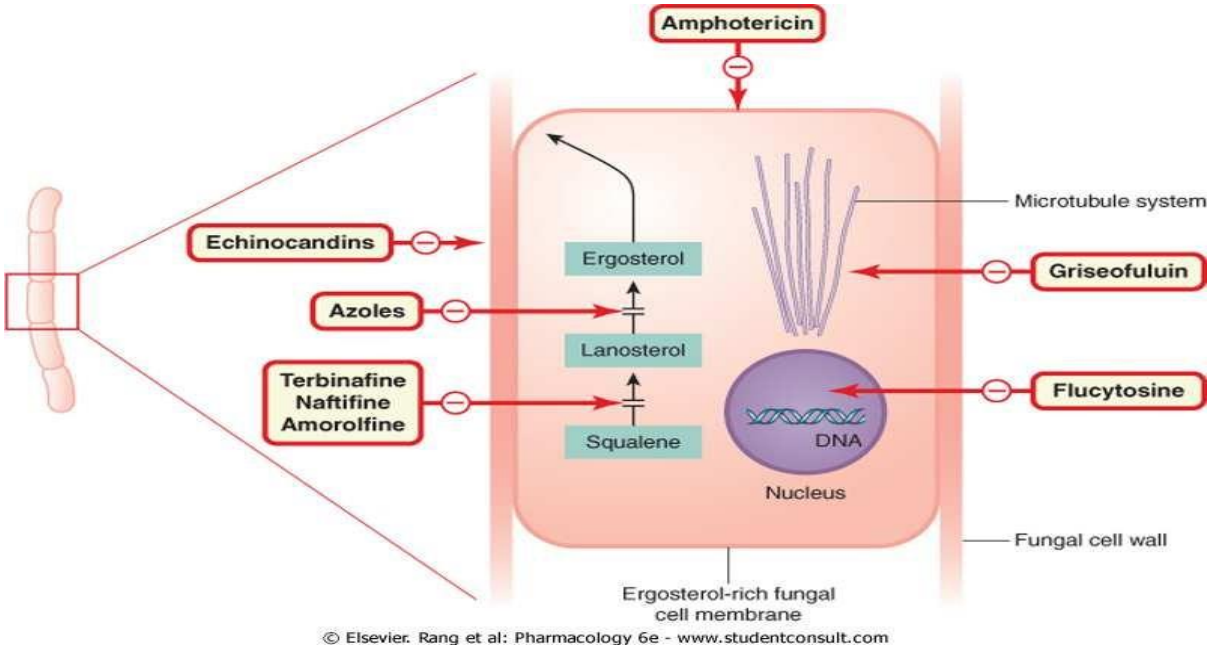


Figure 2: Generalized fungal cell depicting the sites of action of the common antifungal agents.

(3H)-Quinazolinones and their derivatives constitute an important class of heterocyclic compounds. They occupy an important position in medicinal and pesticide chemistry, presenting a wide range of bioactivities. As medicines, many of them display antifungal, antimicrobial, anti- HIV, antitubercular, anticancer, anti-inflammatory, anticonvulsant, antidepressant, hypolipidemic, antiulcer, analgesic or immunotropic activities and are also known to act as thymidylate synthase, poly(ADP-ribose) polymerase (PARP), and protein tyrosine kinase inhibitors. As pesticides, they are used as insecticides, fungicides and antiviral agents such as TMV, CMV inhibitors. In light of the growing number of applications in recent years there has been an enormous increase in the interest among biologists and chemists in their synthesis and bioactivity of quinazolinone derivatives.

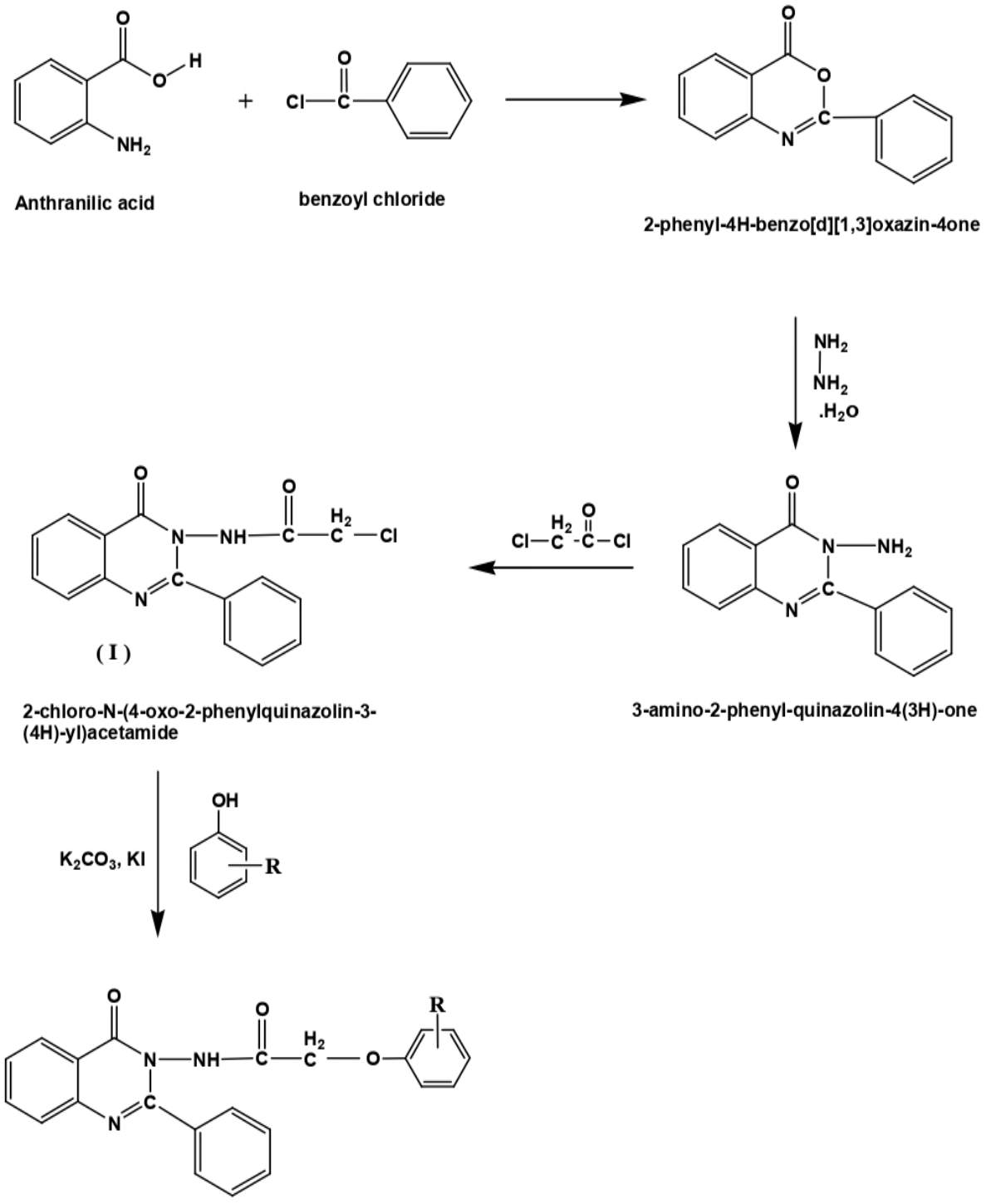
Quinazolinone derivatives[9,10, 11,12,13,14]

Bacterial resistance to existing drugs is a growing problem in the world. Considerable researches have been performed on the synthesis of new quinazolinone derivatives with potent antimicrobial activity. These derivatives possess antibacterial activities, especially against the gram positive strains, and fungi through their interaction with the cell wall and DNA structures.

Structure activity relationship studies of quinazolinone derivatives in various literatures have revealed that substitution at positions 2 and 3, existence of halogen atom at 6 and 8 positions and substitution (mainly amine or substituted amine) at 4th position of the quinazolinone ring can improve their antimicrobial activities. The presence of substituted aromatic ring at position 3 and methyl, amine or thiol groups at position 2 are essential for antimicrobial activities.

2. EXPERIMENTAL SECTION

Synthetic Scheme



The Synthesis of these quinazolinone derivatives can be divided into four parts

1. Synthesis of 2-phenyl-4H-benzo[d] [1, 3] oxazin-4-one.
2. Synthesis of 3-amino-2-phenyl- quinazolin-4(3H)-one.
3. Synthesis of 2-chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide.
4. Synthesis of quinazolinone derivatives using different phenols.

1. Synthesis of 2-phenyl-4H-benzo[d] [1, 3] oxazin-4-one

To a stirred solution of anthranilic acid (0.1 mole, 13.7 g) in pyridine (120 mL), benzoyl chloride (0.1 mole, 11.5 ml) was added drop wise, maintaining the temperature near 0-5 ºC for 1 hour. The reaction mixture was stirred for another 2 hrs at room temperature until a solid product was formed. The reaction mixture was neutralized with saturated sodium bicarbonate solution & the pale yellow solid which separated was filtered, washed with water & recrystallized from ethanol to give the compound.[15]

Yield – 70.23%
Melting point – 113-115 ºC
Mol. Formula – $C_{14}H_9O_2N$
R_f Value – 0.70
Mobile phase for TLC – Petroleum Ether: Ethyl acetate (9:1)

2. Synthesis of 3-Amino-2-phenyl-quinazolin-4(3H)-one

To a stirred solution of 2-phenyl-4H-benzo[d][1,3]oxazin-4-one (0.05 mole, 11.15 g) in pyridine (20 ml), 80% $N_2H_4.H_2O$ (0.15 mole, 7.35 ml) was added. The reaction mixture was stirred & refluxed for half an hour at 117 ºC on an oil bath. After cooling, the crude product was obtained by filtration, washed with water & recrystallized from ethanol.[15]

Yield – 79.48%
Melting point – 176-178 ºC
Mol. Formula – $C_{14}H_{11}ON_3$
R_f Value – 0.71
Mobile phase for TLC – Petroleum Ether: Ethyl acetate (9:1)

3. Synthesis of 2-Chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl) acetamide (I-1)

3-Amino-2-phenyl-quinazolin-4(3H)-one (0.05 mole, 11.85 g) and ethyl methyl ketone (45 ml) were taken in three necked round bottom flask (500 ml) provided with mechanical stirrer, two dropping funnels and was surrounded with a mixture of ice and salt. In one dropping funnel, solution of chloroacetyl chloride (0.05 mole, 3.95 ml) in ethyl methyl ketone (20 ml) was taken and in the other dropping funnel sodium carbonate (5 g) in distilled water (20 ml) was taken. At first some volume of sodium carbonate solution was added to the reaction flask and this was followed by simultaneous drop wise addition of solution of chloroacetyl chloride in ethyl methyl ketone and solution of sodium carbonate from dropping funnels. The temperature of the reaction mixture was kept between 7-10 ºC. At the end of the process of addition, the contents of the flask should be basic (pH 7- 8). The dropping funnels were removed and the contents of the flask were stirred for half an hour at room temperature. The solid so obtained was filtered, washed with water and recrystallized from dimethyl formamide (DMF) to obtain the compound.

To obtain the compound present in filtrate, mixture was transferred into a separating funnel and aq. layer was removed. The organic layer was washed with water and was then transferred to 250 ml conical flask to which sodium sulphate (Na_2SO_4) was added and kept overnight. Then the mixture was filtered and the resulting mixture was concentrated on water bath to yield compound, which was recrystallized from DMF.

Yield – 89.9%
Melting point – 185-186 ºC
Mol. Formula – $C_{16}H_{12}N_3O_2Cl$
R_f Value – 0.68
Mobile Phase for TLC – Chloroform: Methanol (1:2)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Fig.3): 7.71(s, 1H, NH); 6.04-7.03(m, 9H, Ar-H), 3.10(s, 2H, CH_2)

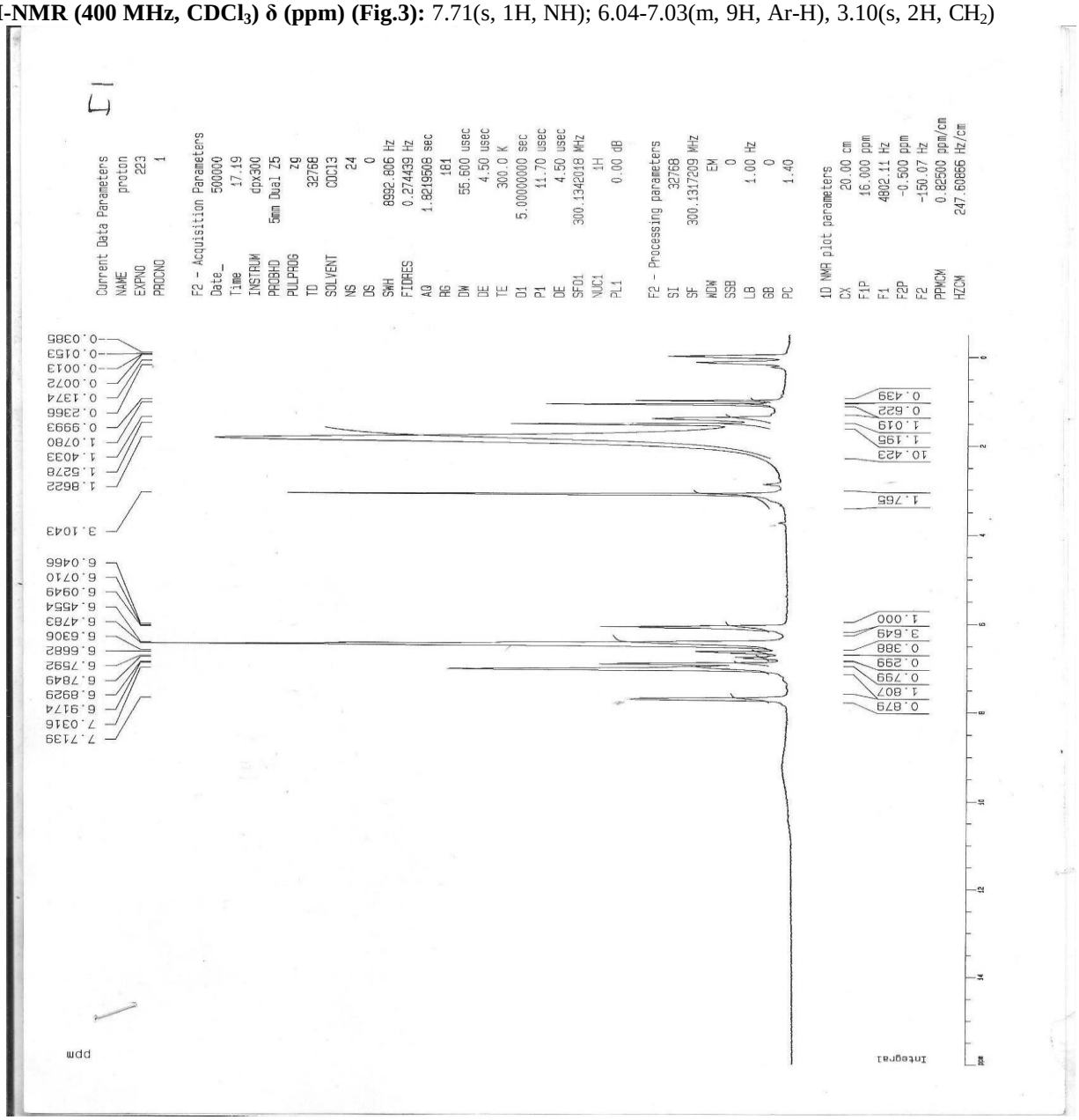
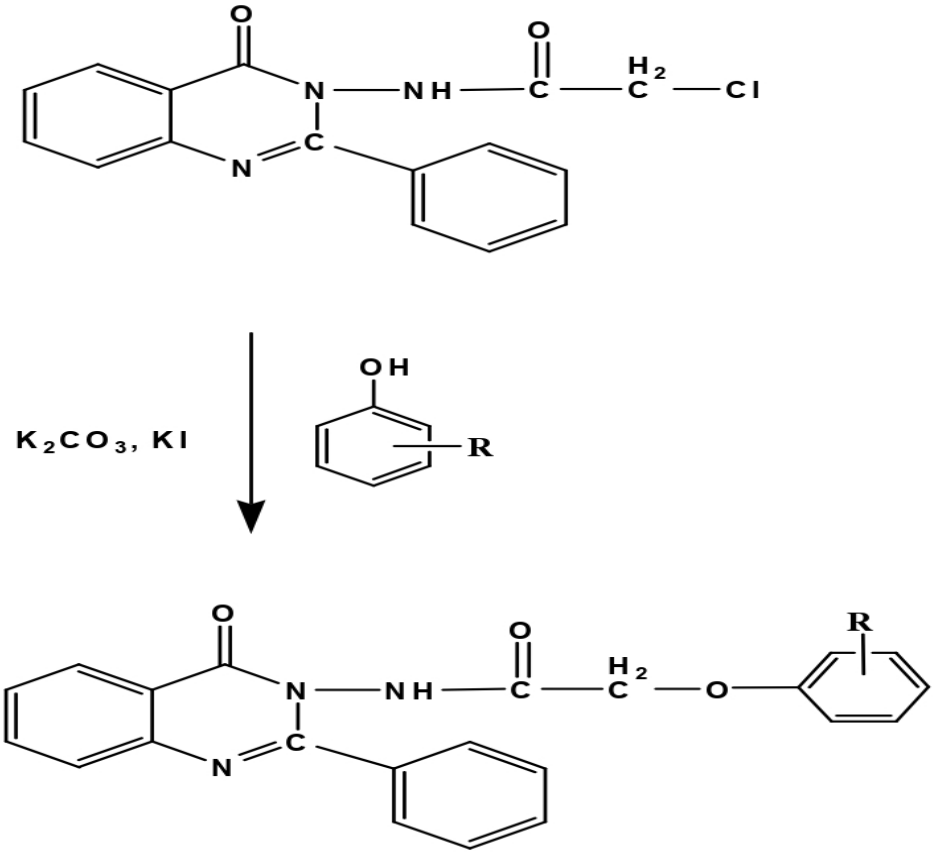


Figure 3: NMR Spectra of 2-Chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (I-1).

4. Synthesis of quinazolinone derivatives using different phenols

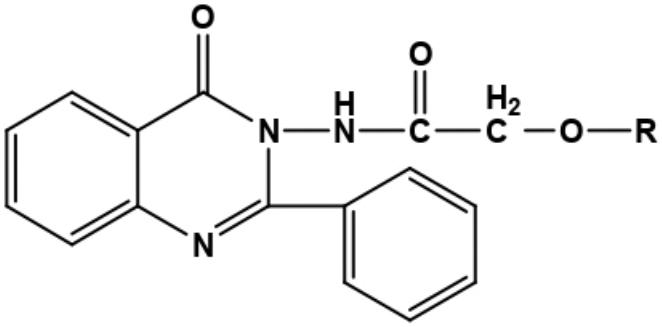
Quinazolinone derivatives were prepared by reacting 2-chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (0.01 mole) with different substituted phenols (0.01 mole) in presence of anhydrous potassium carbonate (0.01 mole), and catalytic amount of potassium iodide in refluxing dry acetone. In some cases unreacted phenol was removed from the final product by treating the substance with 10% Na_2CO_3 solution. The compound was then filtered and washed thoroughly with water and recrystallized from appropriate solvent.

The reaction can be depicted by the following general equation.



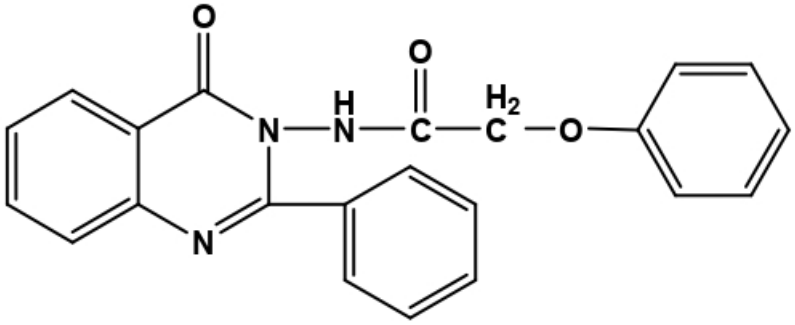
The compounds thus prepared along with their physical constants are listed in Table-1.

Table 1: Physical constants of different Quinazolinone derivatives.



S. No.	Compound code	R	M. P. (ºC)	Yield (%)	Mol. Formula	R_f value
1.	DK-1	C_6H_5	257-258	43.71	$C_{22}H_{17}O_3N_3$	0.80
2.	DK-2	4-NO_2.C_6H_4	260-261	31.63	$C_{22}H_{16}O_5N_4$	0.72
3.	DK-3	4-Cl.C_6H_4	259-260	27.5	$C_{22}H_{16}O_3N_3Cl$	0.69
4.	DK-4	2,6-Cl.C_6H_3	262-263	32.55	$C_{22}H_{15}O_3N_2Cl_2$	0.64
5.	DK-5	2-$COOCH_3$.C_6H_4	250-251	42.85	$C_{24}H_{19}O_5N_3$	0.66
6.	DK-6	4-Cl.3-CH_3.C_6H_3	258-259	38.64	$C_{23}H_{18}O_3N_3Cl$	0.73
7.	DK-7	2-OCH_3.4-CH_2.$CH{=}CH_2$.C_6H_3	263-264	41.86	$C_{26}H_{23}O_4N_3$	0.65

4.1. ***N-(4-oxo-2-phenylquinazolin-3(4H)-yl)-2-phenoxyacetamide(DK-1)***



2-Chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (0.01 mole, 3.1 g), N,N-dimethyl formamide (DMF)(10-15 ml), phenol (0.01 mol, 0.9 g), dry acetone (40 ml), potassium carbonate (0.01 mol, 1.38 g) and catalytic amount of potassium iodide were taken in a three necked RBF provided with mechanical stirrer and reflux condenser. The reaction mixture was refluxed with stirring on water bath for 10 hrs, while progress and completion of the reaction was monitored by TLC. Then, the reaction mixture was transferred to the beaker and water was added to it. The solid which precipitated out was filtered and recrystallized from acetone to yield the compound.

Yield – 43.71%
Melting point – 257-258 ºC
Mol. Formula – $C_{22}H_{17}O_3$ N_3
R_f Value – 0.80
Mobile Phase for TLC – Chloroform:Ethyl acetate (1:1)

IR (KBr) cm^{-1} (Fig.4): 3250.4(N-H), 3067.1(C-H aromatic), 2933(C-H str in CH_2), 1690.6(C=O), 16141.1(ring C=C), 1585(C=N), 1260.3(C-N), 1165.7(C-O-C), 1074.9(N-N)

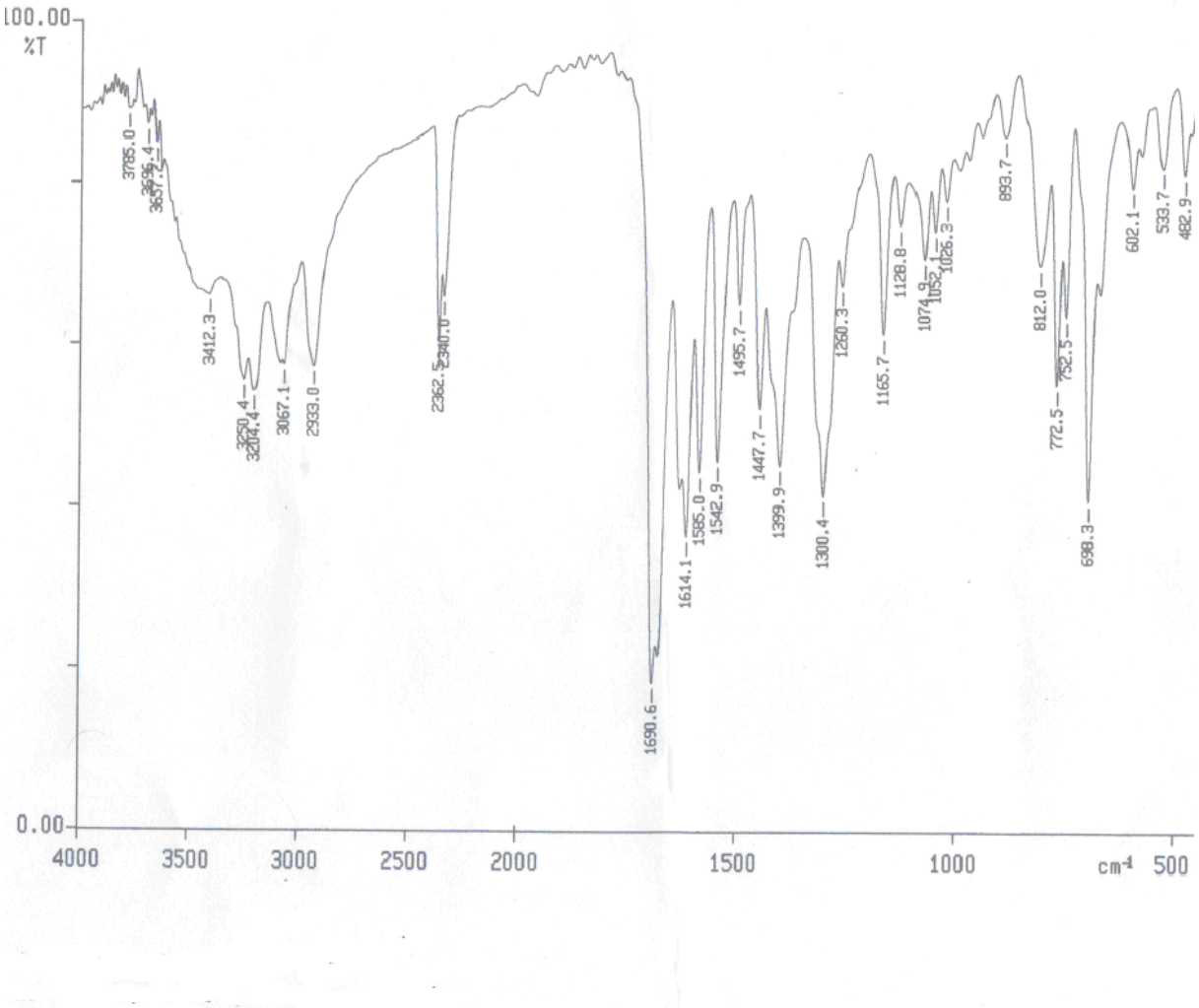
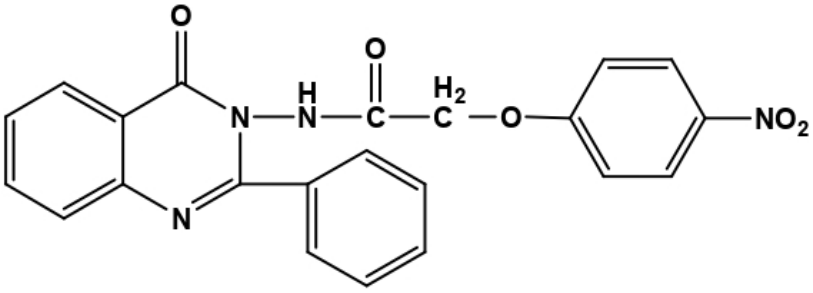


Figure 4: IR Spectra of N-(4-oxo-2-phenylquinazolin-3(4H)-yl)-2-phenoxyacetamide (DK-1).

4.2. ***2-(4-nitrophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (DK-2)***



2-Chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (0.01 mol, 3.1 g), DMF (10-15 ml), 4-nitrophenol (0.01 mole, 1.39 g), dry acetone (40 ml), potassium carbonate (0.01 mol, 1.38 g) and catalytic amount of potassium iodide were taken in a three necked RBF provided with mechanical stirrer and reflux condenser. The reaction mixture was refluxed with stirring on water bath for 12 hrs, while progress and completion of the reaction was monitored by TLC. Then, the reaction mixture was transferred to the beaker and water was added to it. The solid which precipitated out was filtered and recrystallized from acetone to yield the compound.

Yield – 31.63%
Melting point – 260-261 ºC
Mol. Formula – $C_{22}H_{16}O_5N_4$
R_f Value – 0.72
Mobile Phase for TLC – Chloroform: Ethyl acetate (1:1)

IR (KBr) cm^{-1} (Fig.5): 3199.8(N-H), 3065.1(C-H aromatic), 2931.7(C-H str in CH_2), 1689.9(C=O), 1586.2(ring C=C), 1511.5(C=N), 1537.9(NO_2 asym.str), 1300(NO_2 sym. str**),** 1258.4(C-N), 1165(C-O-C), 1026.5(N-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Fig.6): 7.51(s, 1H, NH); 5.64-6.94(m, 13H, Ar-H); 3.51(s, 2H, CH_2)

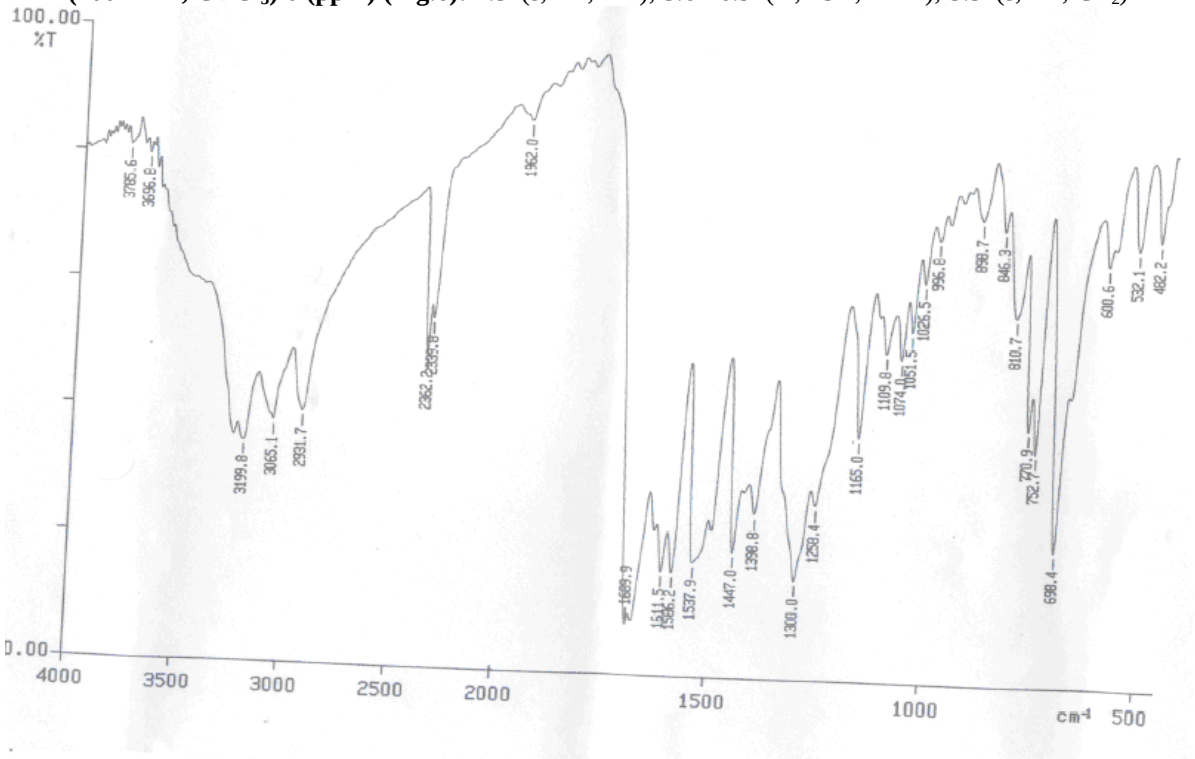


Figure 5: IR Spectra of 2-(4-nitrophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (DK-2)

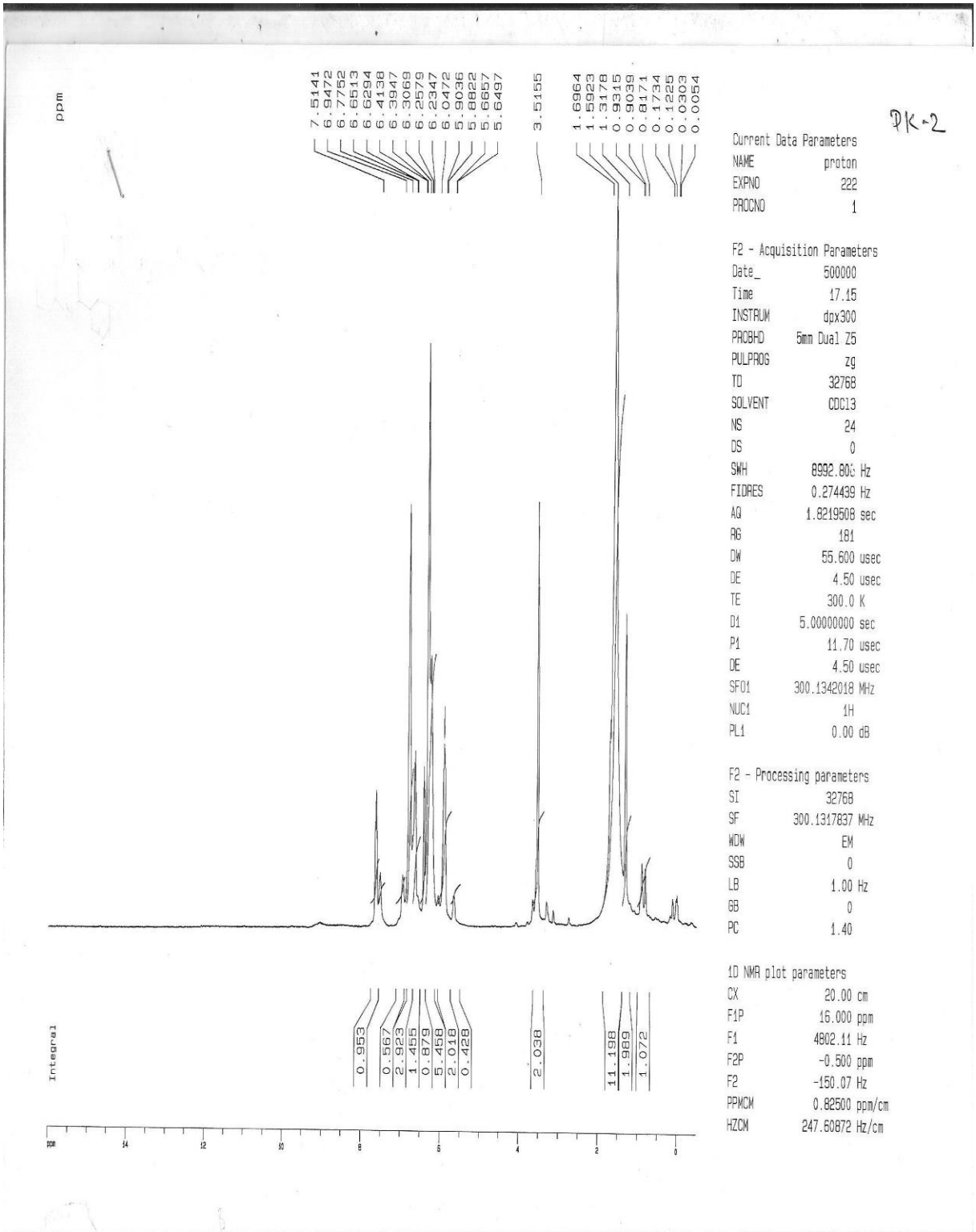
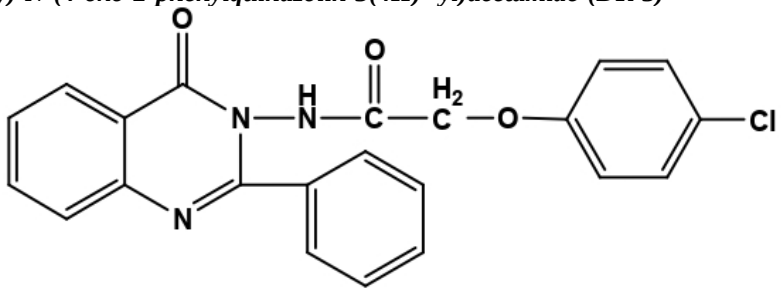


Figure 6: NMR Spectra of 2-(4-nitrophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (DK-2)

4.3. ***2-(4-chlorophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)- yl)acetamide (DK-3)***



2-Chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (0.01 mol, 3.1 g), DMF (10-15 ml), 4-chlorophenol (0.01 mol, 1.28 g), dry acetone 40 ml), potassium carbonate (0.01 mol, 1.38 g) and catalytic amount of potassium iodide were taken in a three necked RBF provided with mechanical stirrer and reflux condenser. The reaction mixture was refluxed with stirring on water bath for 11 hrs, while progress and completion of the reaction was monitored by TLC. Then, the reaction mixture was transferred to the beaker and water was added to it. The solid which precipitated out was filtered and recrystallized from acetone to yield the compound.

Yield – 27.5%

Melting point – 259-260 ºC

Mol. Formula – $C_{22}H_{16}O_3N_3Cl$

R_f Value – 0.69

Mobile Phase for TLC – Chloroform:Ethyl acetate (1:1)

IR (KBr) cm^{-1} (Fig.7): 3201.1(N-H), 3066.3(C-H aromatic), 2922.6(C-H str in CH_2), 1690(C=O), 1541.6(ring C=C), 1613.7(C=N), 1259.7(C-N), 1165.0(C-O-C),1051.7(N-N), 533(C-Cl)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Fig.8): 7.60(s, 1H, NH); 5.90-6.81(m, 13H, Ar-H); 3.56(s, 2H, CH_2)

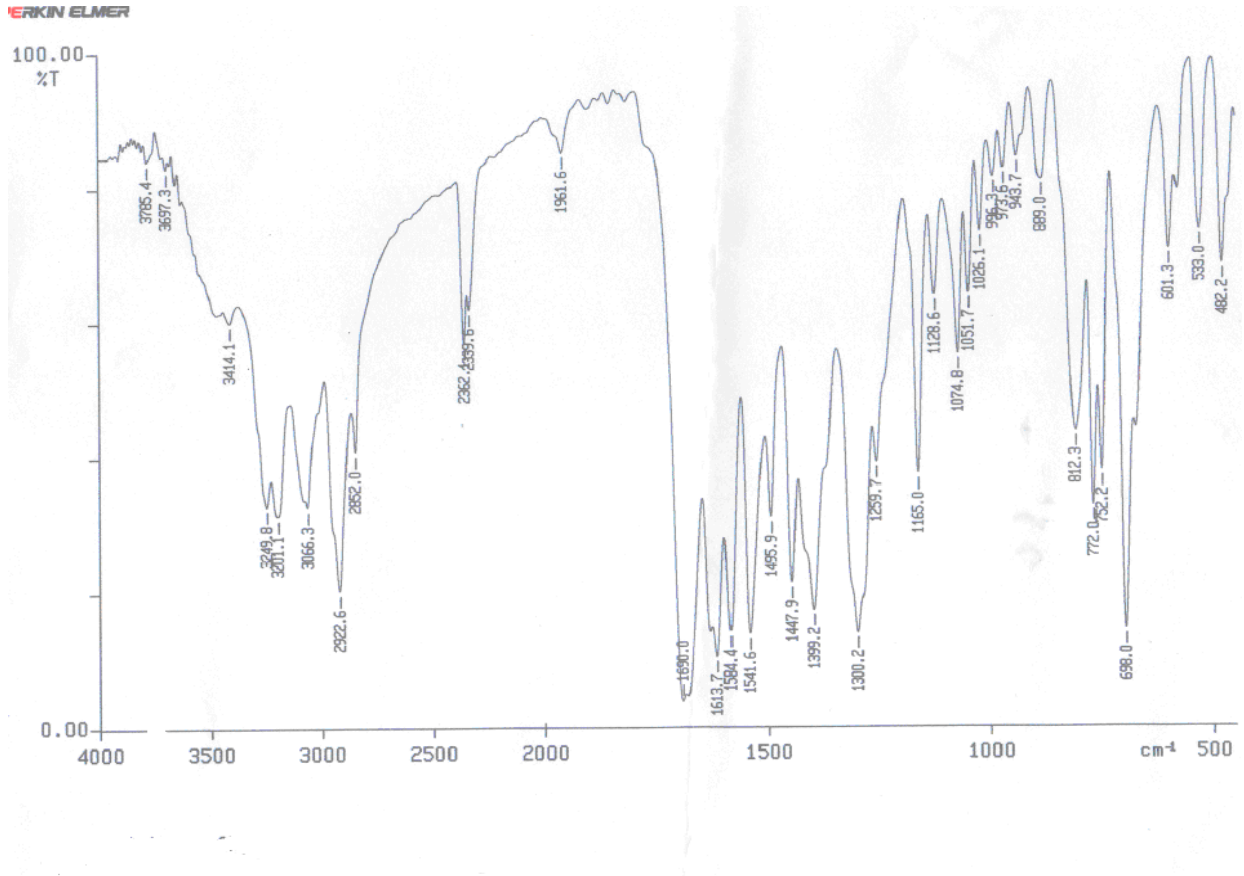


Figure 7: IR Spectra of 2-(4-chlorophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)- yl)acetamide (DK-3).

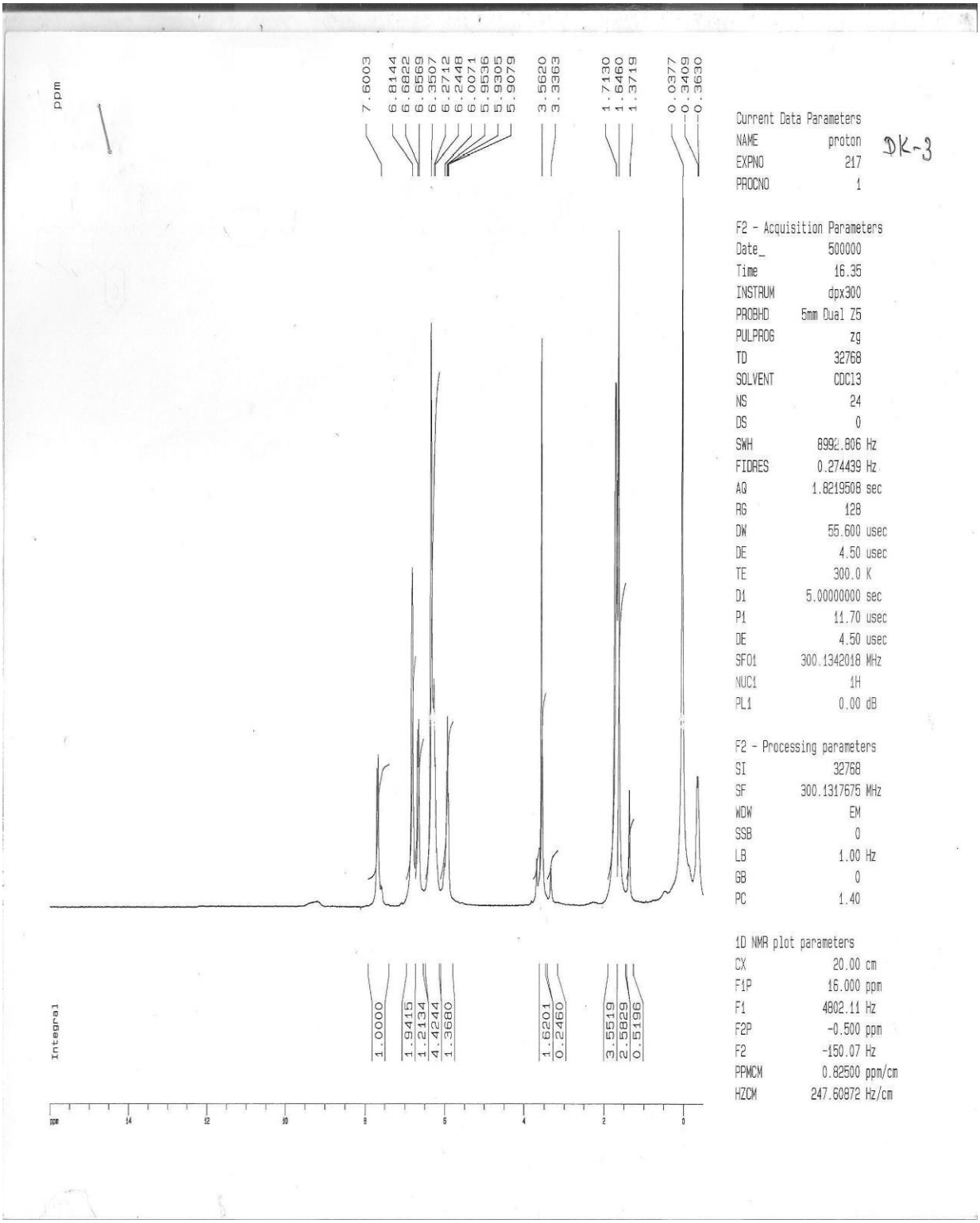
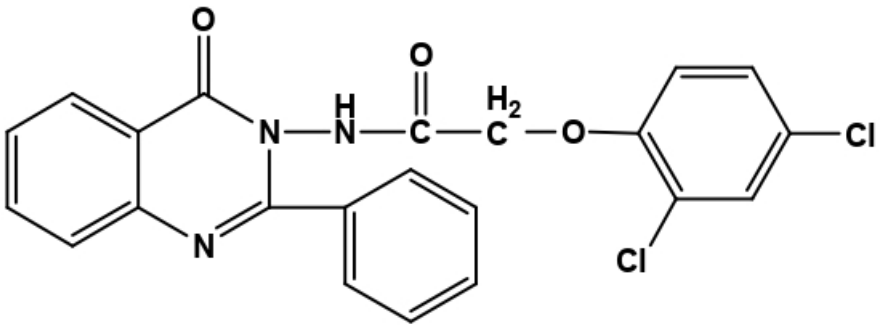


Figure 8: NMR Spectra of 2-(4-chlorophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)- yl)acetamide (DK-3).

4.4. ***2-(2,4-dichlorophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (DK-4)***



2-Chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (0.01 mol, 3.1 g), DMF (10-15 ml), 2,6-dichlorophenol (0.01 mol, 1.63 g), dry acetone 40 ml), potassium carbonate (0.01 mol, 1.38 g) and catalytic amount of potassium iodide were taken in a three necked RBF provided with mechanical stirrer and reflux condenser. The reaction mixture was refluxed with stirring on water bath for 10 hrs, while progress and completion of the reaction was monitored by TLC. Then, the reaction mixture was transferred to the beaker and water was added to it. The solid which precipitated out was filtered and recrystallized from acetone to yield the compound.

Yield – 32.55%

Melting point – 262-263ºC

Mol. Formula – $C_{22}H_{15}O_3N_2Cl_2$

R_f Value – 0.64

Mobile Phase for TLC – Chloroform: Ethyl acetate (1:1)

IR (KBr) cm^{-1} (Fig.9): 3248.5(N-H), 3065.3(aromatic C-H), 2930.2(C-H str in CH_2), 1690.7(C=O), 1584.1(ring C=C), 1613.4(C=N), 1259.8(C-N), 1164.7(C-O-C), 1074.3(N-N), 532.3(C-Cl)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Fig.10): 8.83(s, 1H, NH); 7.02-7.94(m, 12H, Ar-H); 4.68(s, 2H, CH_2)

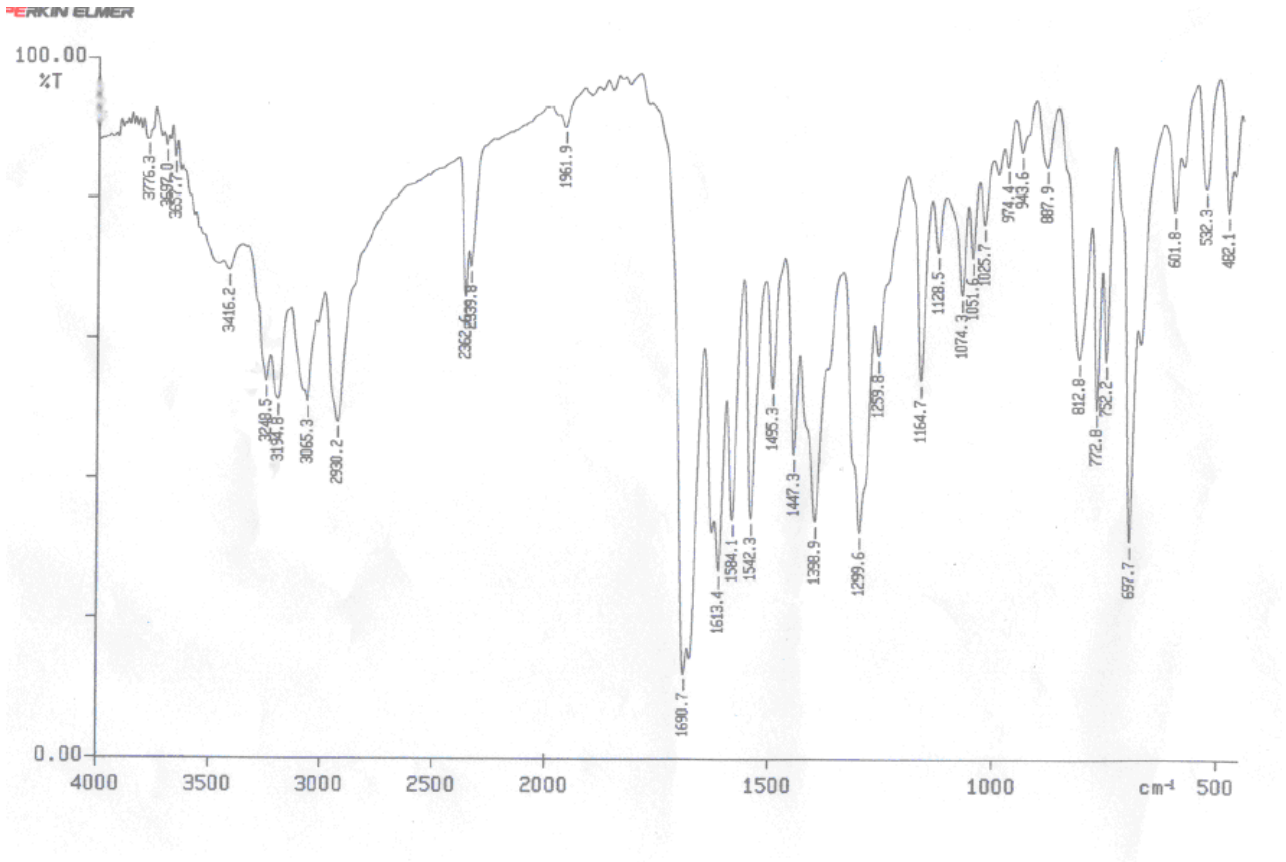


Figure 9: IR Spectra of 2-(2,4-dichlorophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (DK-4)

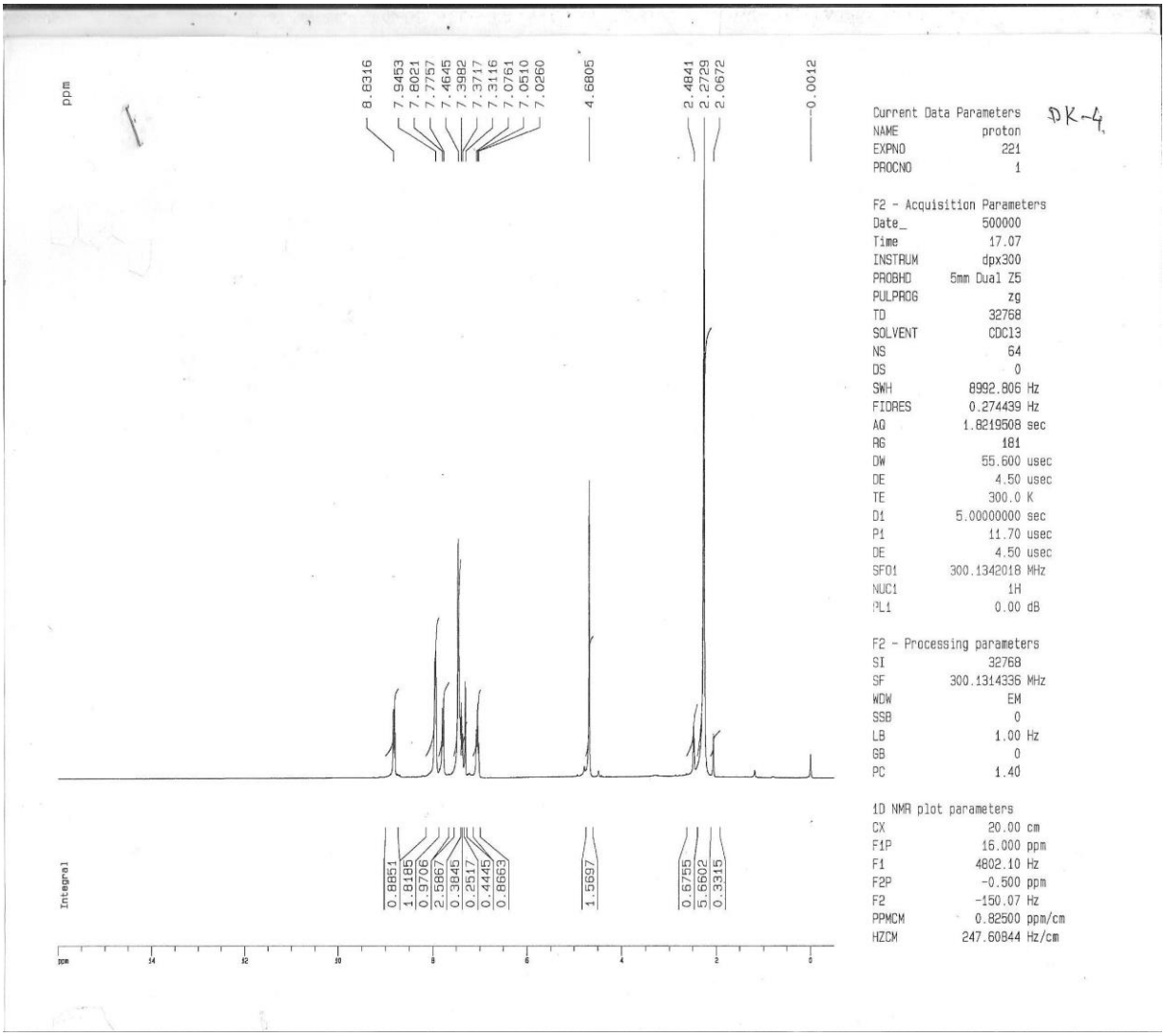
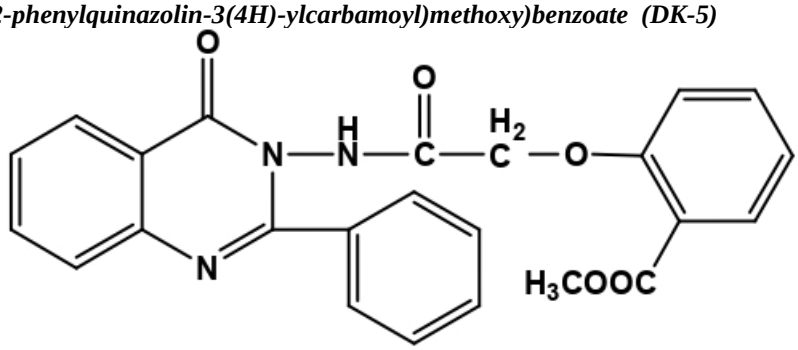


Figure 10: NMR Spectra of 2-(2,4-dichlorophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (DK-4).

4.5. ***Methyl-2-((4-oxo-2-phenylquinazolin-3(4H)-ylcarbamoyl)methoxy)benzoate (DK-5)***



2-Chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (0.01 mol, 3.1 g), DMF (10-15 ml), methylsalicylate (0.01 mol, 1.28 ml), dry acetone (40 ml), potassium carbonate (0.01 mol, 1.38 g) and catalytic amount of potassium iodide were taken in a three necked RBF provided with mechanical stirrer and reflux condenser. The reaction mixture was refluxed with stirring on water bath for 13 hrs, while progress and completion of the reaction was monitored by TLC. Then, the reaction mixture was transferred to the beaker and water was added to it. The solid which precipitated out was filtered and recrystallized from acetone to yield the compound.

Yield – 42.85%

Melting point – 250-251ºC

Mol. Formula – $C_{24}H_{19}O_5N_3$

R_f Value – 0.66

Mobile Phase for TLC – Chloroform:Ethyl acetate (1:1)

IR (KBr) cm^{-1} (Fig.11): 3221(N-H), 3021(C-H aromatic), 2926.1(C-H str in CH_2), 1680.8(C=O), 1541.3(ring C=C), 1580.5(C=N), 1216.2(C-N), 1141.3(C-O-C),1026.9(N-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Fig.12): 8.0(s, 1H, NH); 6.24-7.96(m, 13H, Ar-H); 3.66(s, 2H, CH_2); 3.90(s, 3H, CH_3)

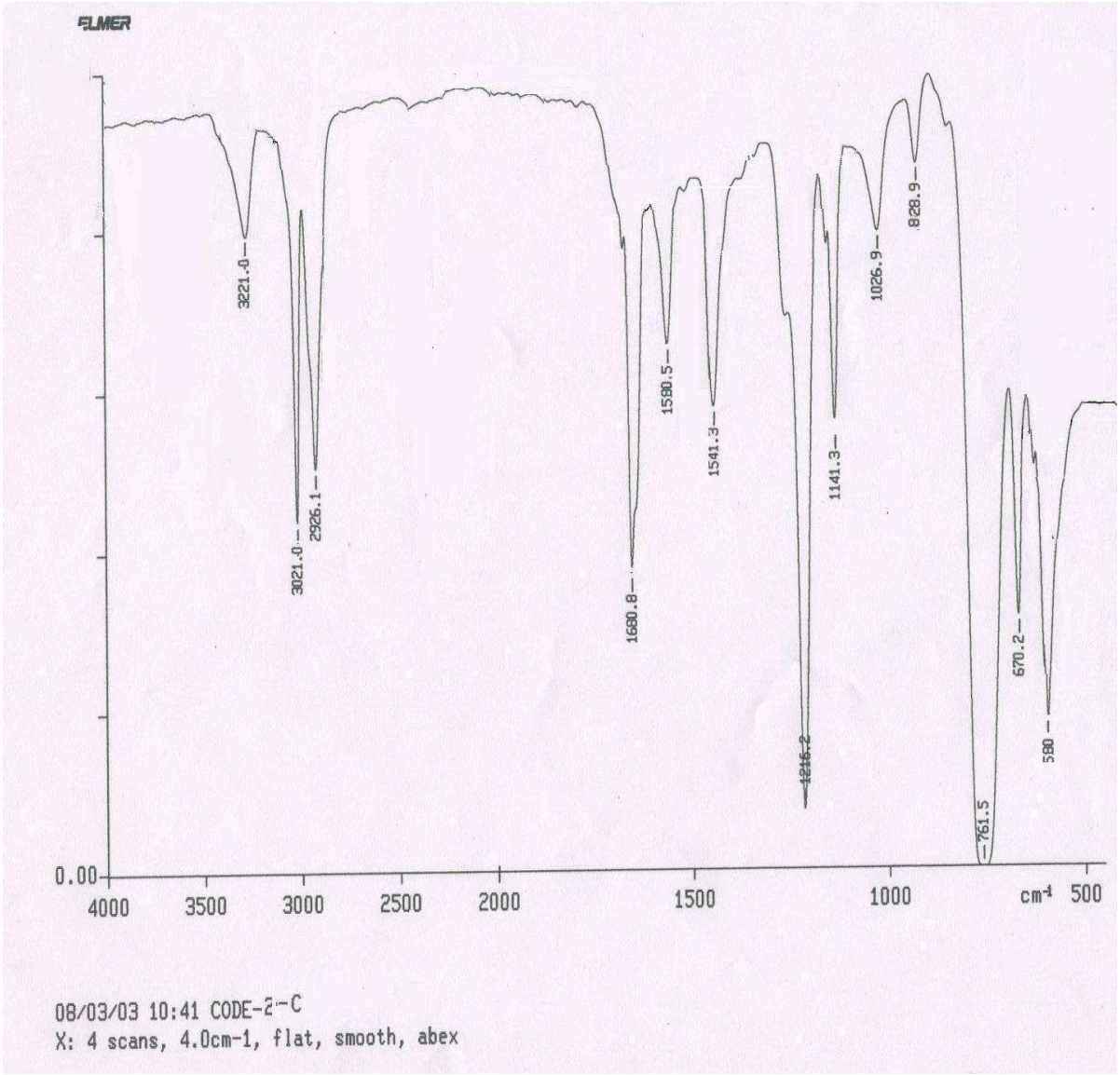


Figure 11: IR Spectra of Methyl-2-((4-oxo-2-phenylquinazolin-3(4H)-ylcarbamoyl)methoxy)benzoate (DK-5)

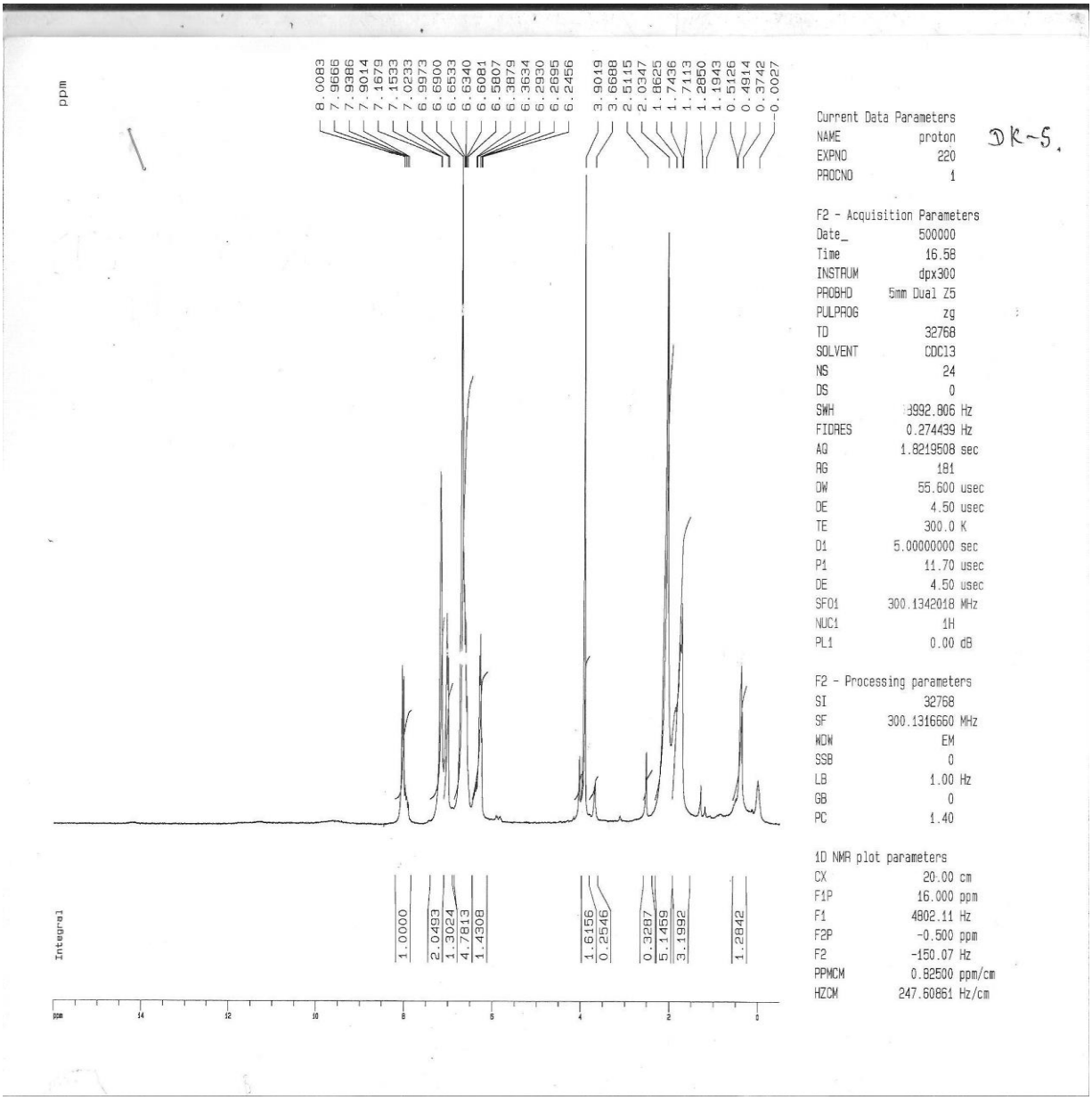
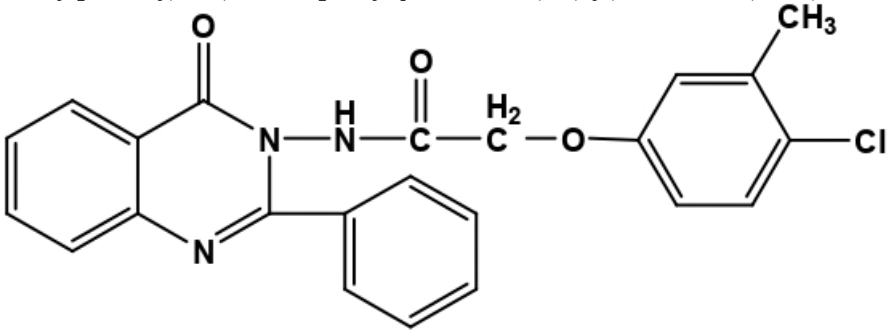


Figure 12: NMR Spectra of Methyl-2-((4-oxo-2-phenylquinazolin-3(4H)-ylcarbamoyl)methoxy)benzoate (DK-5).

4.6. ***2-(4-chloro-3-methylphenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (DK-6)***



2-Chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (0.01 mol, 3.1 g), DMF (10-15 ml), p-chloro-m- cresol (0.01 mol, 1.42 g), dry acetone (40 ml), potassium carbonate (0.01 mol, 1.38 g) and catalytic amount of potassium iodide were taken in a three necked RBF provided with mechanical stirrer and reflux condenser. The reaction mixture was refluxed with stirring on water bath for 14 hrs, while progress and

completion of the reaction was monitored by TLC. Then, the reaction mixture was transferred to the beaker and water was added to it. The solid which precipitated out was filtered and recrystallized from acetone to yield the compound.

Yield – 38.64%

Melting point – 258-259ºC

Mol. Formula – $C_{23}H_{18}O_3N_3Cl$

R_f Value – 0.73

Mobile Phase for TLC – Chloroform:Ethyl acetate (1:1)

IR (KBr) cm^{-1} (Fig.13): 3066.3(C-H aromatic), 248(N-H), 2933.2(C-H str in CH_2), 1690.8(C=O), 1541.8(ring C=C), 1613.9(C=N), 1259.5(C-N), 1165.1(C-O-C), 1026.1(N-N), 533.4(C-Cl)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Fig.14): 7.65(s, 1H, NH); 5.86-6.78(m, 12H, Ar-H); 3.52(s, 2H, CH_2); 1.79(s, 3H, CH_3)

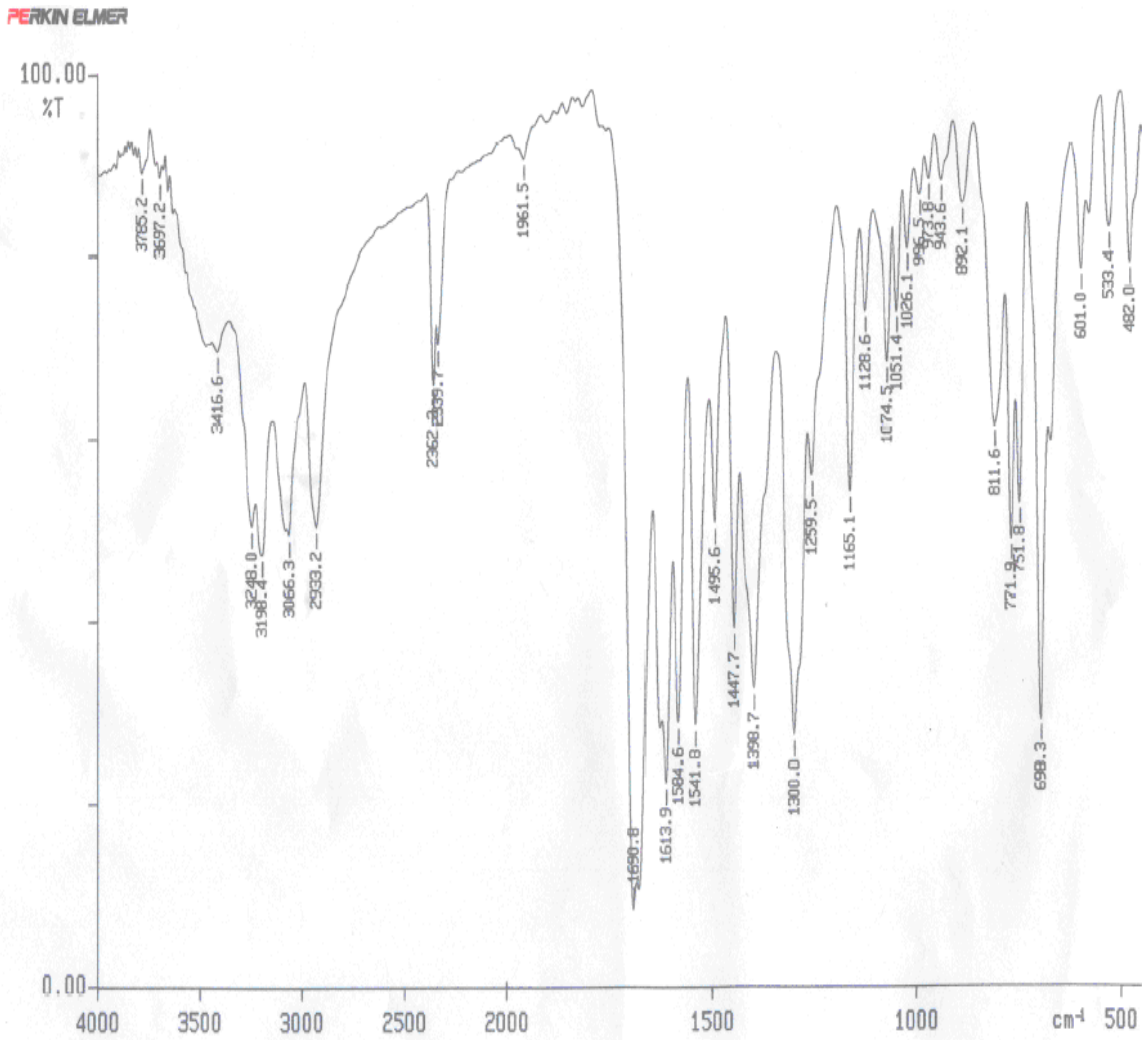


Figure 13: IR Spectra of 2-(4-chloro-3-methylphenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (DK-6)

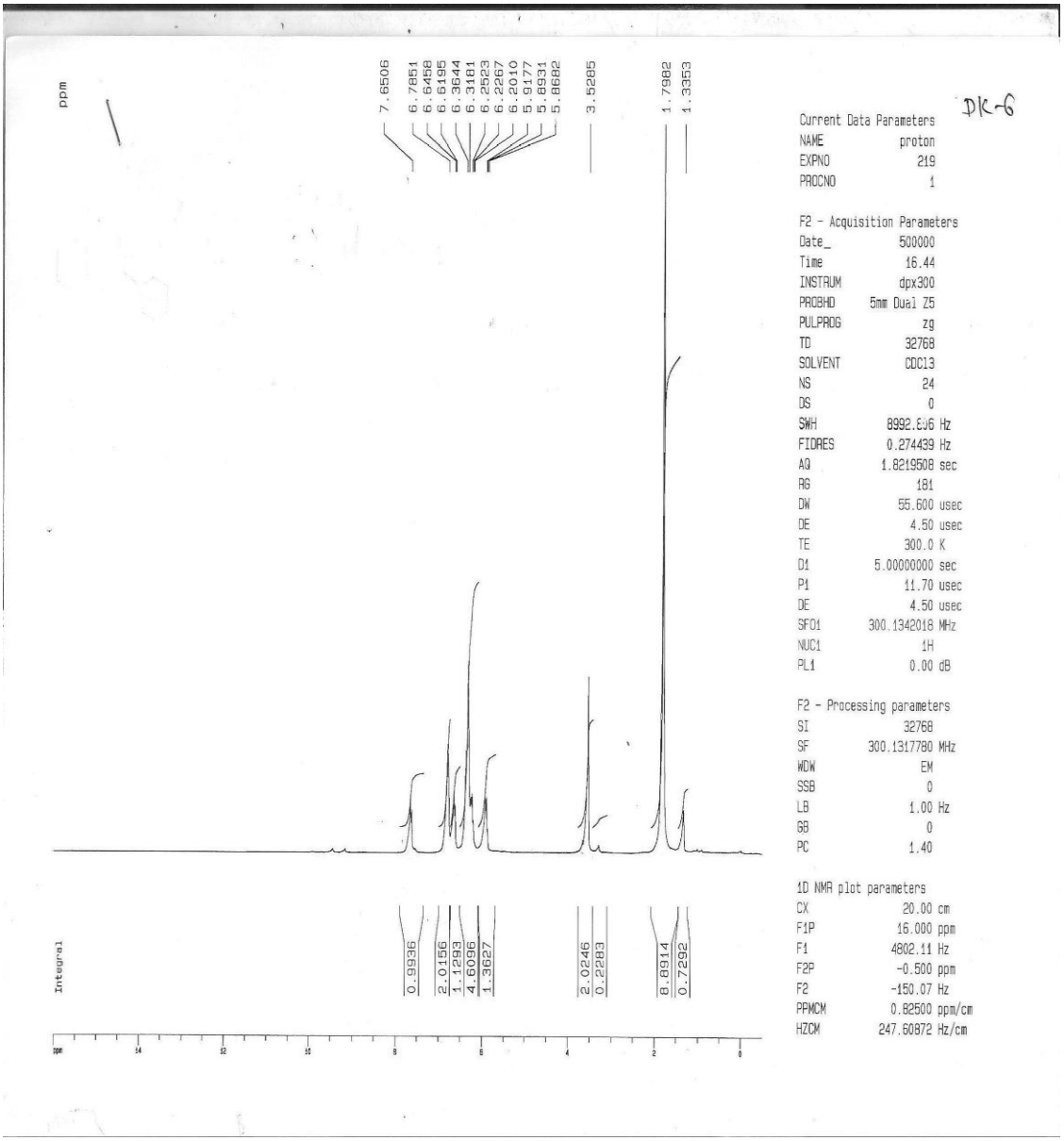
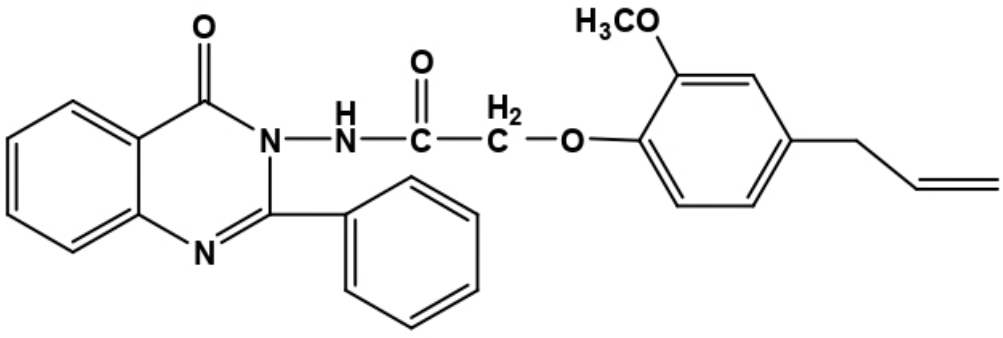


Figure 14: NMR Spectra of 2-(4-chloro-3-methylphenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)- yl)acetamide (DK-6)

4.7. ***2-(4-allyl-2-methoxyphenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide(DK-7)***



2-Chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (0.01 mol, 3.1 g), DMF (10-15 ml), eugenol (0.01 mol, 1.54 ml), dry acetone (40 ml), potassium carbonate (0.01 mol, 1.38 g) and catalytic amount of potassium iodide were taken in a three necked RBF provided with mechanical stirrer and reflux condenser. The reaction mixture was refluxed with stirring on water bath for 12 hrs, while progress and completion of the

reaction was monitored by TLC. Then, the reaction mixture was transferred to the beaker and water was added to it. The solid which precipitated out was filtered and recrystallized from acetone to yield the compound.

Yield – 41.86%
Melting point – 263-264ºC
Mol. Formula – $C_{26}H_{23}O_4N_3$
R_f Value – 0.65
Mobile Phase for TLC – Chloroform:Ethyl acetate (1:1)

IR (KBr) cm^{-1} (Fig.15): 3216.5(N-H), 3020.1(C-H aromatic), 2926.5(C-H str in CH_2), 1726.5(C=O), 1603.9(ring C=C), 1652.9(C=N), 1215.8(C-N), 1144.5(C-O-C), 928.7(N-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) (Fig.16): 8.79(s, 1H, NH); 7.05-7.96(m, 12H, Ar-H); 4.71-4.73(d, 2H, CH_2^* of CH_2^*-CH=CH_2)

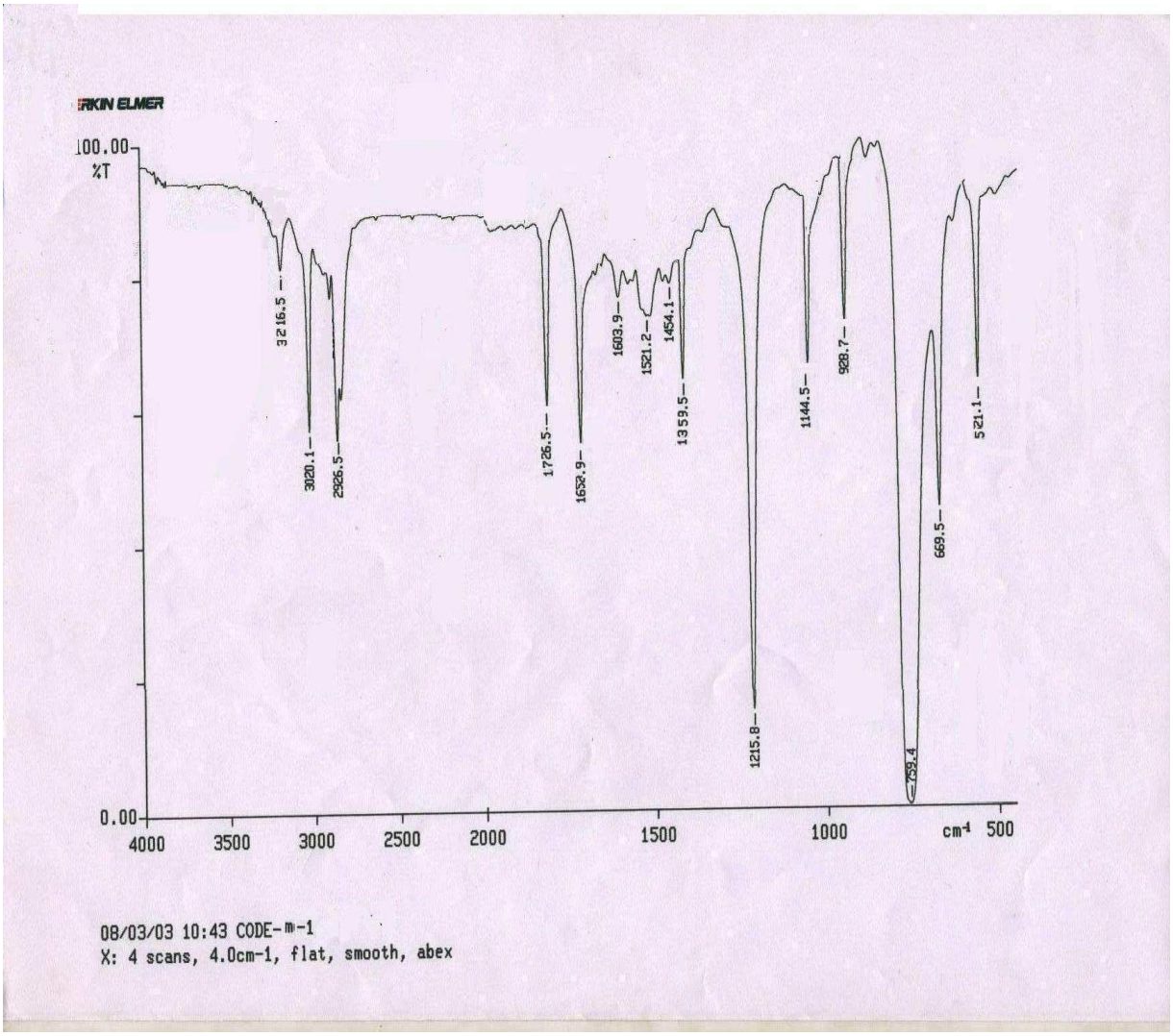


Figure 15: IR Spectra of 2-(4-allyl-2-methoxyphenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (DK-7)

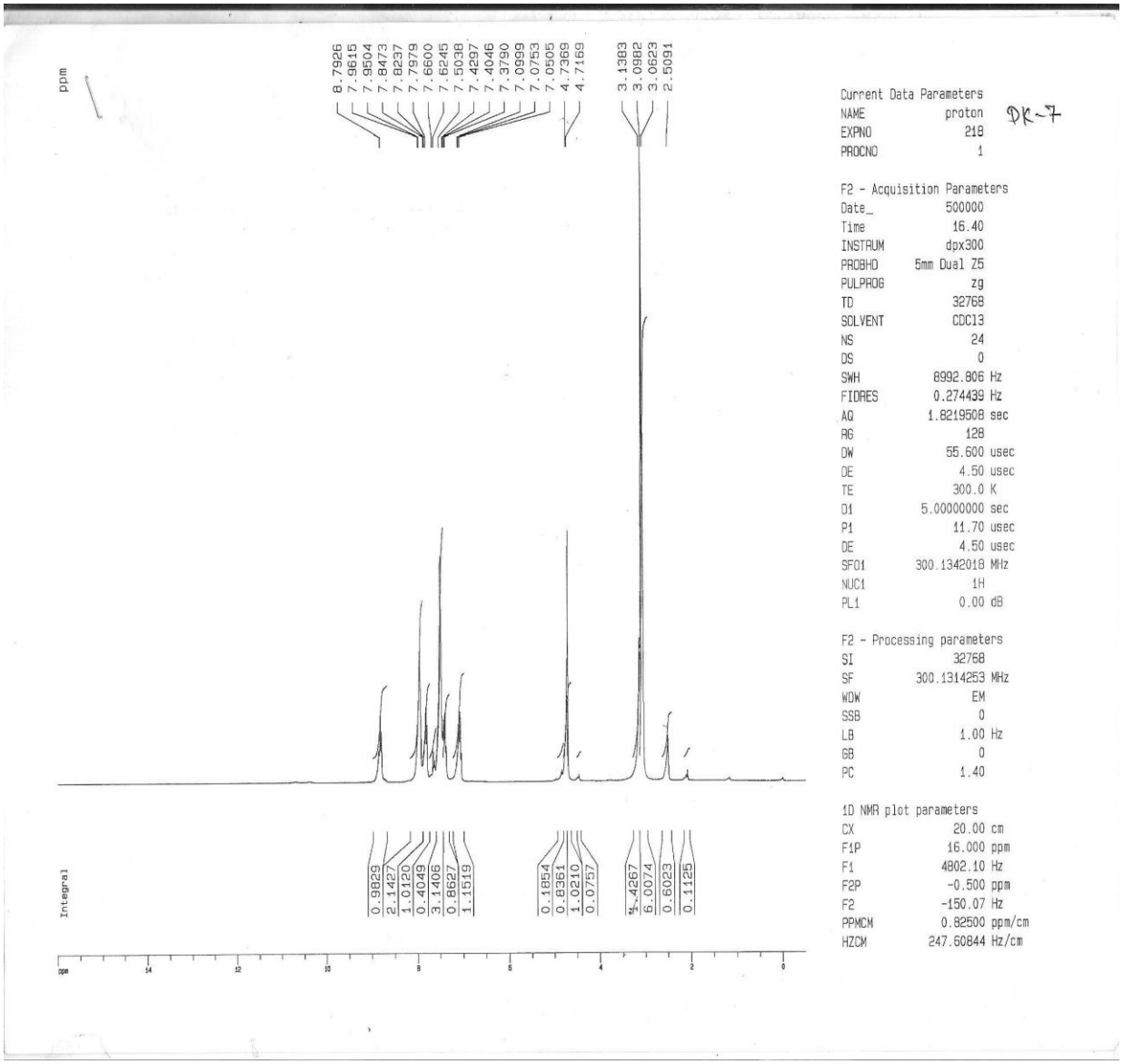


Figure 16: NMR Spectra of 2-(4-allyl-2-methoxyphenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl) acetamide (DK-7)

3. PHARMACOLOGICAL EVALUATION

Earlier studies have shown that quinazolinone derivatives possess antibacterial and antifungal activities. So, an effort was made to check the antibacterial and antifungal activities of the synthesized compounds.

3.1. Antibacterial Activity[16, 17,18,19,20,21,22]

The antibacterial activity of the synthesized compounds was determined by cup plate method by measuring inhibition zone.

MATERIALS

Test strains

S.aureus (209p) E.coli (ESS 2231)

Composition of media

Nutrient agar was used for the purpose which contains the constituents as presented in the Table-2.

Table-2: Composition of Nutrient Agar Medium.

Ingredients	Quantity
Peptone	10g
Beef Extract	10 g
NaCl	5 g
Agar	20 g
Distilled water	upto 1000 ml

Standard Drug and Test Compounds

Ampicillin was used as standard drug at a concentration of 100 g/ml.

Test compounds (DK-1, DK-2, DK-3, DK-4, DK-5, DK-6 and DK-7) were treated at a concentration of 100 g/ml.

DMF was used as solvent control.

METHODOLOGY

Following steps were followed for determination of antibacterial activity of synthesized compounds.

- Laminar airflow bench was swapped with 70 % alcohol and UV lamp was switched on. After 30 min, the UV lamp was switched off.
- All the reagents, media, inoculum and glassware were placed in laminar airflow bench observing all aseptic conditions.
- 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 inoculum 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 ^{0}C for 24 hours. The zone of inhibition was measured using mm scale.
- Negative controlled plate- In this plate, only nutrient agar medium was poured i.e. it did not contain drug dilution and inoculum.
- Positive controlled plate- In this plate, nutrient agar medium was poured and after its solidification, inoculum was spreaded over the surface. But this petriplate did not contain drug solution.

RESULTS AND DISCUSSION

The results of antibacterial activity are reported in Table 3.

Table 3: Antibacterial activity data of synthesized compounds.

S.N.	Compound Code	Zone of inhibition (mm)	
		***S. aureus* (209p)**	***E. coli* (ESS 2231)**
1.	DK-1	10	12
2.	DK-2	18	17
3.	DK-3	6	9
4.	DK-4	8	10
5.	DK-5	7	6
6.	DK-6	10	13
7.	DK-7	11	8
8.	Control	-	-
9.	Standard	15	16

From the antibacterial activity data, it was found that the synthesized compounds exhibited mild to good antibacterial activity against S. aureus (gram-positive) and E. coli (gram-negative) at a concentration of 100µg/ml. The compound DK-2 showed maximum zone of inhibition (18mm) against S. aureus as well as against E. coli (17mm) which is higher than the standard drug Ampicillin. The standard drug (Ampicillin) gave 15mm zone of inhibition against S. aureus (209p) and 16mm zone of inhibition against E. coli (ESS 2231) respectively. The solvent control i.e DMF did not show any activity.

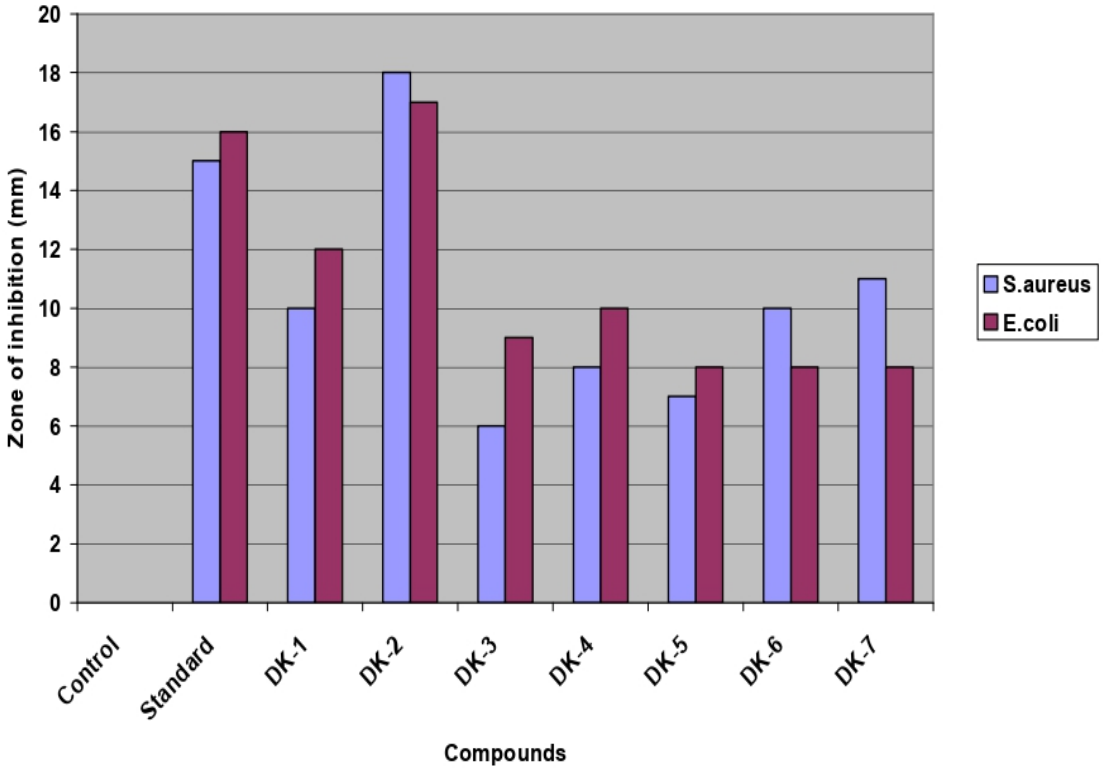


Figure 17: Antibacterial activity of synthesized compounds.

3.2. Antifungal Activity[16, 18,19,20,21,22, 23,24]

All the synthesized compounds were evaluated for their antifungal activity against Aspergillus niger and Candida albicans (ATCC 10231) using Fluconazole as standard drug by cup plate method. We had adopted the same method as described in section 5.2.1 except the culture medium and incubation period. Sabouraud dextrose agar was used as culture medium and the plates were incubated at 25°C for 48 hours. The standard and test compounds were treated at a concentration of 100µg/ml.

RESULTS AND DISCUSSION

The results of antifungal activity are reported in Table 4.

Table 4: Antifungal activity data of synthesized compounds.

S.No.	Compound Code	Zone of inhibition (mm)	
		A. niger	*C. albicans (ATCC 10231)*
1.	DK-1	8	7
2.	DK-2	10	12
3.	DK-3	12	11
4.	DK-4	9	8
5.	DK-5	13	9
6.	DK-6	15	13
7.	DK-7	14	10
8.	Control	-	-
9.	Standard	25	22

From the antifungal activity data, it was found that the synthesized compounds exhibited mild to moderate antifungal activity against A. niger and C. albicans at a concentration of 100µg/ml. The standard drug

(Fluconazole) gave 25mm zone of inhibition against A. niger and 22mm zone of inhibition against C. albican (ATCC 10231) respectively. The solvent control i.e DMF did not show any activity.

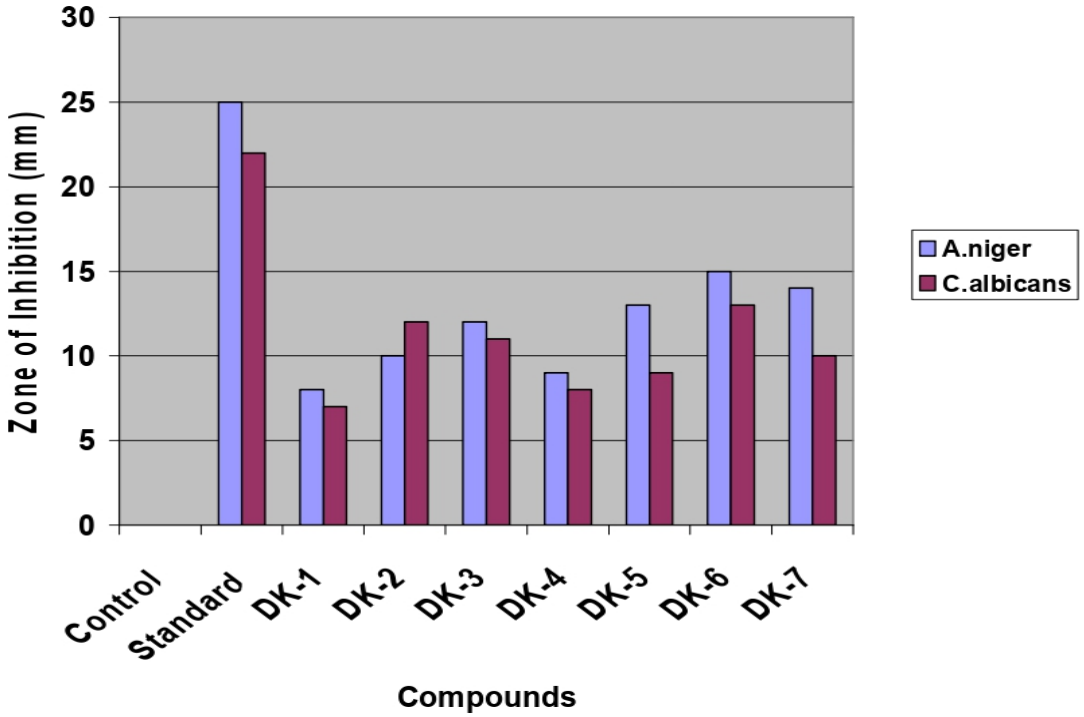


Figure 18: Antifungal activity of synthesized compounds.

4. RESULTS AND DISCUSSION

A series of Quinazolinone derivatives (DK-1, DK-2, DK-3, DK-4, DK-5, DK-6 & DK-7) were synthesized by reacting 2-chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide with different substituted phenols in presence of anhydrous potassium carbonate and catalytic amount of potassium iodide in dry acetone. The identity of the compounds was confirmed on the basis of their Melting Point, TLC, IR and ^{1}H-NMR data.

All the synthesized compounds have been tested for antibacterial and antifungal activities by cup plate method. The compounds showed mild to good antibacterial activity and mild to moderate antifungal activity. The compound DK-2 showed more antibacterial activity than the standard drug ampicillin. The compounds showed mild to good antibacterial and antifungal activity.

The present study reveals that some quinazolinone derivatives could be used as a template for the future development through modification or derivatization to design more potent therapeutic agents.

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