COMPARATIVE STUDIES OF MOLECULAR MODIFICATION APPROACH TO ENHANCE THE SOLUBILITY OF GEFITINIB

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ABSTRACT

Gefitinib is an anticancer drug that belongs to the anilino-quinoline class. It belongs to the BCS class II category, having low solubility and limited oral bioavailability. Antioxidants (*i.e.* gallic acid, benzoic acid, nicotinic acid, oxalic acid, and ascorbic acid) were used to create anticancer derivatives, and the derivatives were combined with API Gefitinib. Formation of Gefitinib Prodrug take place. Then increasing the solubility of the drug. It is also widely used in the treatment of lung and breast cancer. By increasing the solubility of the drug, Gefitinib prodrug shows the best results as compared to Gefitinib drug. Then these compounds' activities were characterised by IR spectra, mass spectra, and ^{1}HNMR spectra. Then, after spectral study, these compounds were used to formulate formulations of tablets by the compression method and perform important solubility enhancing tests like disintegration tests, dissolution tests, and friability tests. By increasing the solubility of the drug, Gefitinib prodrug shows the best results as compared to Gefitinib drug. It is also widely used in the treatment of lung and breast cancer.

This study's objective was to prepare novel synthesised anticancer compounds for combination with Gefitinib medications by synthesising, purifying, characterising, and testing their biological activity. A literature review on anticancer derivatives was conducted in the library to achieve the goal (journals, chemical database search, and internet database search) (sci finder, online sites). So, in order to achieve the goals, I conducted a thorough literature review up to 2021. Then a proposed reaction strategy for derivatives. Thionyl chloride was used in the first step to produce 3,4,5-trihydrobenzoyl chloride (1), (*R*)-5-((*R*)-2-chloro-1-hydroxyethyl)-3,4-dihydroxyfuran-2(5*H*)-one (2), nicotinoyl chloride (3), benzoyl chloride (4), and 2-chloro-2-oxoacetic acid (5). and these were clubbed with gefitinib drugs and formed a compound (6a-e). All the reaction was monitored through TLC observation till their completion using suitable each time. After the completion of the reaction, the products were dried and solvents e.g. methanol was used in final procedure. Additionally, these products are characterised by FTIR, NMR, and mass spectra.

After the formulation of the tablets Check the solubility and stability. According to all these tests, we formed that the 1st formulation was the best formulation of the gefitinib prodrug which enhanced the solubility as compared to other and mainly gefitinib drugs.

1. INTRODUCTION:

1.1 Cancer:

Cancer is a condition when a few of the body's cells grow out of control and spread to other part of the body. Cancer is a complex illness. It is a collection of around 200 distinct diseases. One of the main causes of mortality in affluent nations, cancer is a complex illness [1]. Changes (mutations) to the DNA within cells are what lead to cancer. A cell's DNA is organised into numerous distinct genes, each of which carries a set of instructions directing the cell's performance of certain tasks as well as its growth and division. Incorrect instructions can make a cell cease functioning normally and even give it the chance to develop cancer [2]. The second greatest cause of death worldwide is cancer. On the other hand, because to advancements in cancer detection, treatment and prevention of survival rates are rising for many cancer types. There are numerous cancer treatments available [3]. Your cancer's type and stage, overall health, and personal preferences are just a few of the variables that will affect your treatment options. Your doctor and you can evaluate the advantages and disadvantages of each cancer treatment to decide which is best for you.

1.2. Lung Cancer: One type of cancer that starts in the lungs is lung cancer. Your lungs are two pliable organs located in your chest that allow you to breathe in oxygen and exhaust carbon dioxide. The largest cause of cancer-related fatalities worldwide is lung cancer [4]. Lung cancer can affect persons who have never smoked, but smokers are at a higher risk than non-smokers. The quantity and frequency of cigarettes you have smoked are related to your chance of developing lung cancer. Your risk of developing lung cancer can be considerably decreased if you stop smoking, even after smoking for a long time [5].

- **Symptoms:** In its early stages, lung cancer often exhibits no signs or symptoms. Lung cancer signs and symptoms often appear when the condition is advanced [6].

  Lung cancer symptoms and signs may include:

  - Losing weight without trying
  - A new cough that won't go away
  - Coughing up blood, even a little bit of it
  - Shortness of breath
  - Chest discomfort

- Hoarseness
- Bone pain
- Headache

1.2.1. Treatments:

The treatment prescription is made upon the basis of type and stage of cancer. In most cases, combination therapy is employed [7]. Treatments can be broadly categorized as local and systemic depending upon their targeted mechanism.

Table 1.1: Comparison between local and systemic treatment

	Local treatment	**Systemic treatment**
Targeted area	Designed to remove cancer cells where they originated.	Designed to treat cancer cells wherever they may present in the body
Treatments Included	Surgery, Radiation therapy	Chemotherapy, Targeted therapies, Immunotherapy

1.3. Prodrug:

Even though the concept of a prodrug was first described in the late 1950s, prodrugs have been around for much longer. Aspirin, which was first marketed in 1899, was one of the first widely used prodrugs [8]. When it enters the body, it transforms into salicylic acid. Researchers have developed various prodrugs to enhance medications over the years. They can help to improve the effectiveness of a medication or prevent certain side effects [9].

- Prodrugs are drug molecules that are chemically or enzymatically transformed in vivo to produce the active parent drug with the desired pharmacologic properties. Prodrugs are widely used to improve absorption, distribution, metabolism, and excretion (ADME) processes [10]. Prodrug is an inactive form of drug which needs conversion in the body to one or more of its metabolites. The metabolites form is the one which is active and is capable of producing the desired reaction [11].

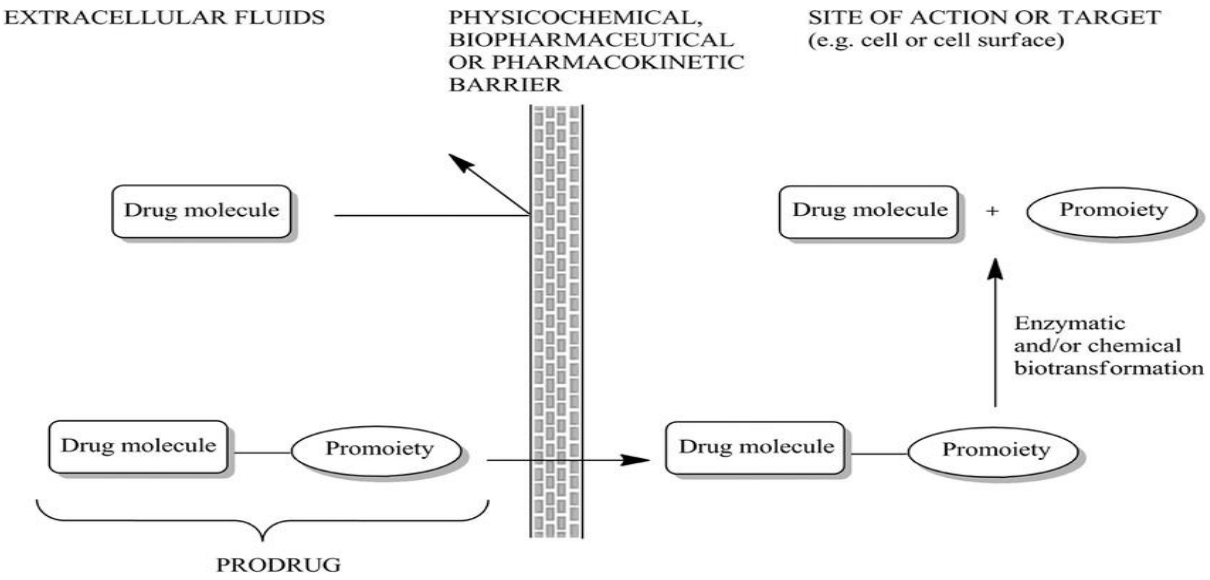


Figure 1.1: Schematic representation of prodrug and its metabolism.

1.4. Gefitinib Drug:

The medication gefitinib is used to treat non-small cell lung cancer. It is utilised in individuals with faulty epidermal growth factor receptor (EGFR) genes, cancer that has progressed to other regions of the body, and who have not received prior cancer treatment [12].

- **May Treat:** Non-small cell lung cancer.
- **Brand Names**: Geftinat · Geftilon · Gefitero · Geffy · Xefta · Zufinib · Gefitec · Geftib
- **Drug Class:** Tyrosine kinase inhibitors (Quinazolinamines).
- **Pregnancy:** CONSULT YOUR DOCTOR- Gefitinib is unsafe to use during pregnancy. Please consult your doctor.
- **Lactation**: CONSULT YOUR DOCTOR- Gefitinib is probably unsafe to use during lactation.
- **Alcohol:** UNSAFE - It is unsafe to consume alcohol with Gefitinib.
- **Driving:** UNSAFE - Gefitinib may cause side effects that affect your ability to drive.
- **Liver Warning:** SAFE IF PRESCRIBED - Gefitinib is probably safe to use in patients with liver disease. Please consult your doctor.
- **Kidney Warning:** CAUTION - Gefitinib should be used with caution in patients with severe kidney disease. Please consult your doctor.
- **Addiction:** Not known to be addictive.

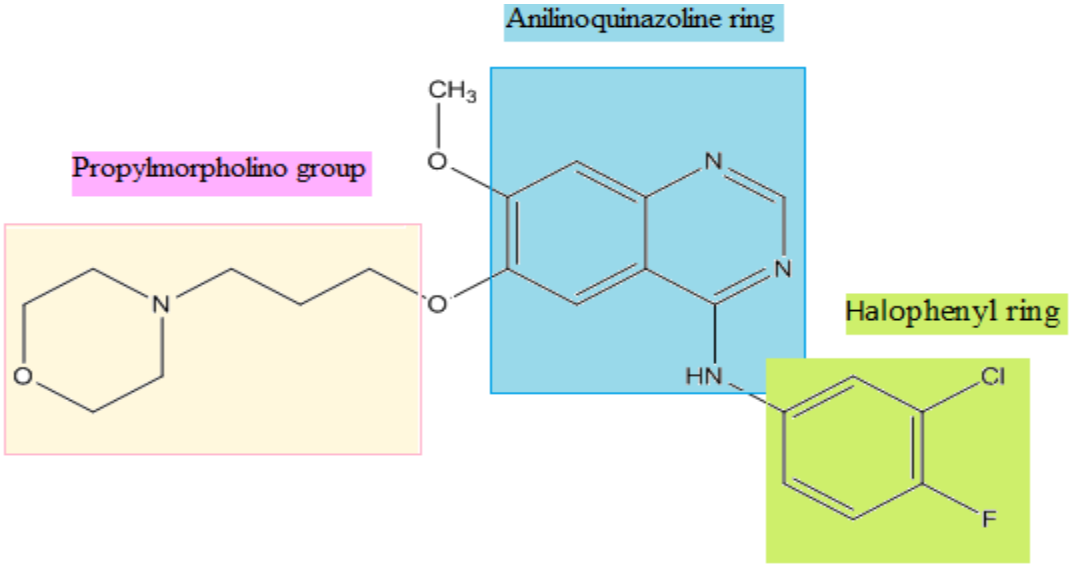


Figure 1.2: Gefitinib functional groups

- Present work is focused on implementation of Prodrug of anticancer drug, gefitinib (GEF) with the aim to tune its biopharmaceutical properties. Gefitinib (GEF), a is an anticancer drug with belongs to aniliniquinazoline class[13]. And is an orally administrated chemotherapy treatment for lung and breast cancers which inhibit the activity of the epidermal growth factor receptor (EGFR) of protein (tyrosine kinase) that has shown activity in non-small-cell lung cancer (NSCLC).

Table 1.2: Physicochemical characterization of gefitinib

	Solubility	Melting point
Test Specification Data obtained	• DMSO - 20 mg/ml • Ethanol - 0.3 mg/ml • DMSO - very soluble • Ethanol - slightly soluble • Methanol - freely soluble • Water - insoluble	• 193℃ to 197℃ • 193℃ to 195℃

1.4.1. Mechanism of Action:

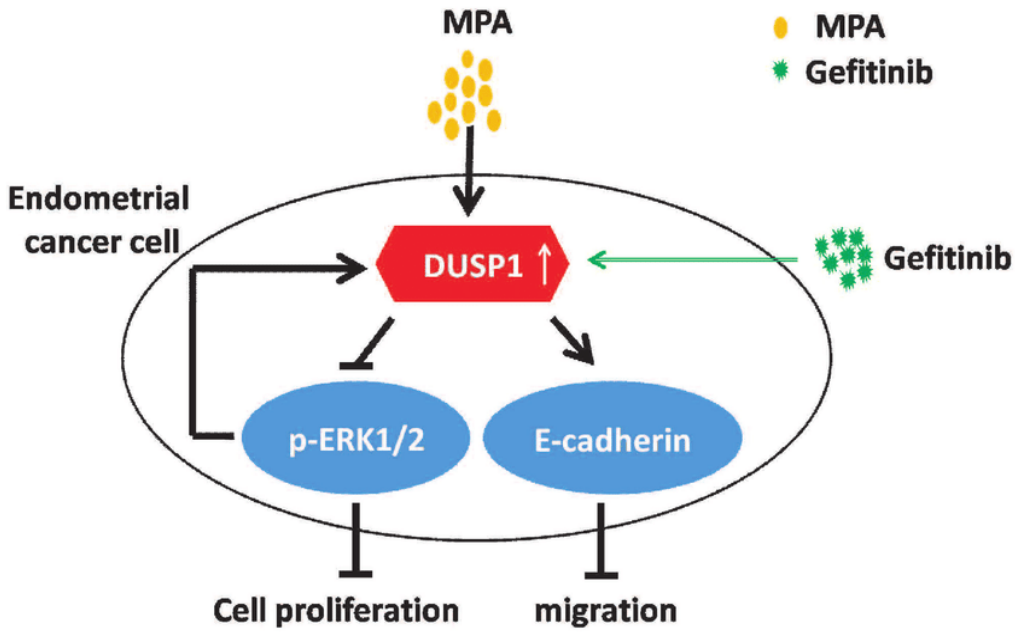


Figure 1.3: MOA of Gefitinib Drug

- Gefitinib (GEF), a is an anticancer drug with belongs to aniliniquinazoline class. And is administrated orally. Gefitinib, a potent and selective ATP-competitive inhibitor of EGFR and HER-2 kinases, is the first EGFR-targeting agent launched as an anticancer drug in Japan, Australia, and the United Sates for the treatment of chemo resistant non-small cell lung cancer (NSCLC) patients. In preclinical studies, gefitinib has demonstrated antitumor activity against a variety of human cancer cell lines expressing EGFR, including lung, ovarian, breast, and colon [14]. The epidermal growth factor receptor (EGFR) protein tyrosine kinase is one of the important kinases that play a fundamental role in signal transduction pathways. Many human cancers overexpress EGFR and the related human epidermal growth factor receptor (HER-2). Compounds, such as gefitinib, that inhibit the kinase activity of EGFR. HER-2 after binding of their cognate ligand, have been used as new therapeutic antitumor agents [15].
- Also, its potential value in the treatment of central nervous system (CNS) metastases has been rarely assessed. But Gefitinib has major problem of solubility, dissolution and stability of the drug. It was approved for clinical use in 2003. It belongs to BCS class II category having low solubility limited oral bioavailability [16]. A traditional design of anticancer prodrugs uses the covalent modification by hydrophilic functionalities (e.g. phosphate, sulfate) and lipophilic moieties (e.g. ester) for increasing the aqueous solubility and passive permeability respectively[17]. Several techniques such as nanoparticles, liposomes and suspension formulation have been employed to improve its poor biopharmaceutical properties, however, they have their own limitations [18].

History:

It is a white-coloured free base belonging to **BCS II** class thereby indicating high permeability and low solubility Gefitinib is sparingly soluble at pH 1 and practically insoluble above pH 7, with the solubility decreasing sharply between pH 4 and pH 6. It is freely soluble in glacial acetic acid and dimethyl sulfoxide, soluble in pyridine, sparingly soluble in tetrahydrofuran, and slightly soluble in methanol, ethanol (99.5%), ethyl acetate, propan-2-ol and acetonitrile [19]. The molecule has pKa value of 5.4 and 7.2.

Gefitinib is marketed as IRESSA by Astra Zeneca Pharmaceuticals and is available as brown film-coated tablet, containing 250 mg of gefitinib, for oral administration [20].

1.5. Antioxidant: Any substance that can inhibit the formation of unstable molecules known as free radicals, which harm DNA, cell membranes, and other components of cells, is referred to be an antioxidant. Free radicals are countered by antioxidants by sacrificing some of their own electrons [21].

The main antioxidants which are used in the synthesis of gefitinib prodrug are given below:

i. Gallic Acid: Chemical formula: $C_7H_6O_5$, Molecular Weight: 170.12 g/mol

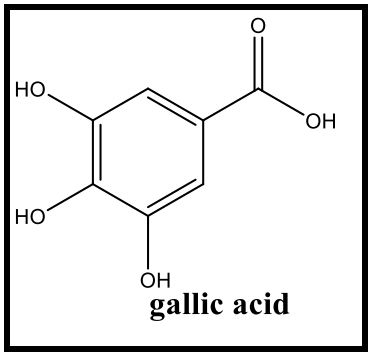


Figure 1.4: Structure of Gallic Acid

ii. Ascorbic Acid: Chemical formula: $C_6H_8O_6$, Molecular Weight: 176.12 g/mol

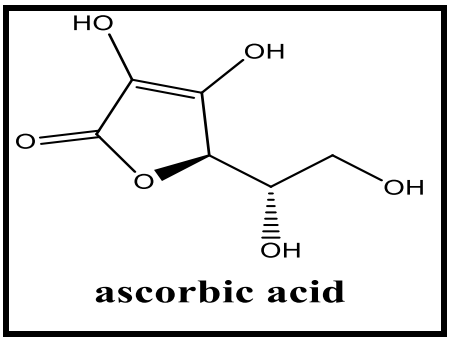


Figure 1.5: Structure of Ascorbic Acid

iii. Nicotinic Acid: Chemical formula: $C_6H_5NO_2$ or C_5H_4NCOOH, Molecular Weight: 123.11 g/mol

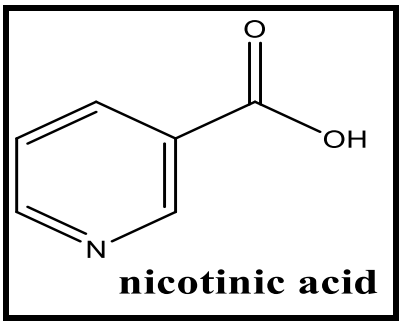


Figure 1.6: Structure of Nicotinic Acid

iv. Benzoic Acid: Chemical formula: C_6H_5COOH, Molecular Weight: 127.15 g/mol

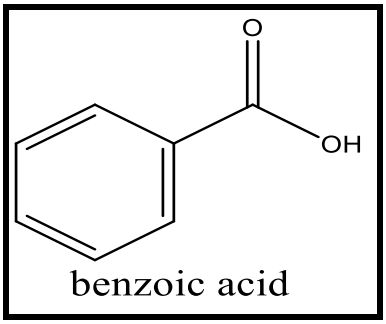


Figure 1.7: Structure of Benzoic Acid

v. **Oxalic Acid:** Chemical formula: $C_2H_2O_4$ or $(COOH)_2$, Molecular Weight: 90.03 g/mol

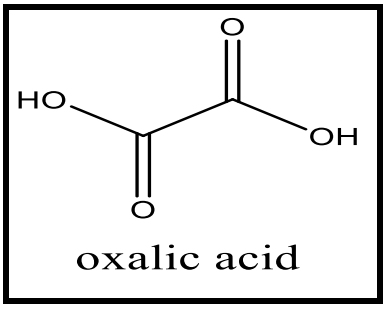


Figure 1.8: Structure of Oxalic Acid

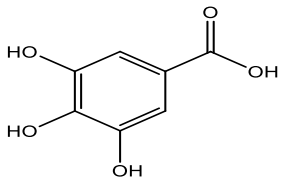
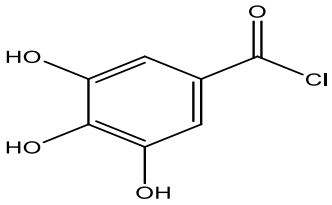
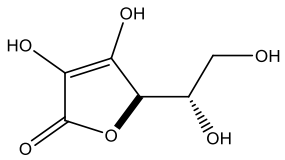
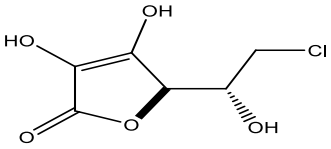
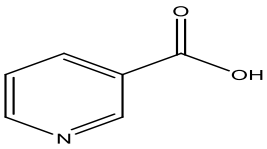
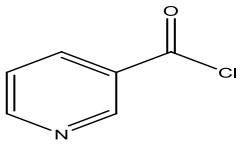
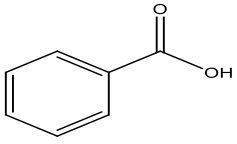
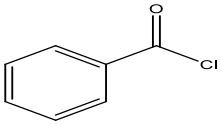
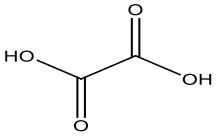
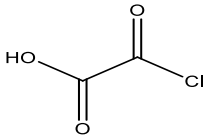
- Five Prodrugs of gefitinib have been prepared with highly soluble gallic acid (GAL), ascorbic acid (AA), nicotinic acid, benzoic acid and oxalic acid antioxidant of (Generally Recognized as Safe) GRAS status to improve its solubility, dissolution and finally bioavailability [22].
- These novel prodrugs have been characterized using different analytical techniques differential scanning calorimetry (DSC), Fourier transform infrared spectrometry (FT-IR), powder X-ray diffraction (PXRD) and hot stage microscopy (HSM) and further subjected to solubility, dissolution, pharmacokinetics to assess the potential of this technique in improvement of its physicochemical parameters. Further, evaluation studies involving solubility, dissolution, Log P, pharmacokinetic [23].

2. PLAN OF WORK:

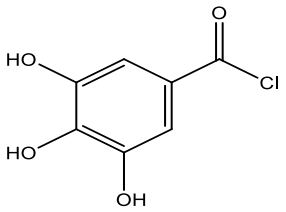
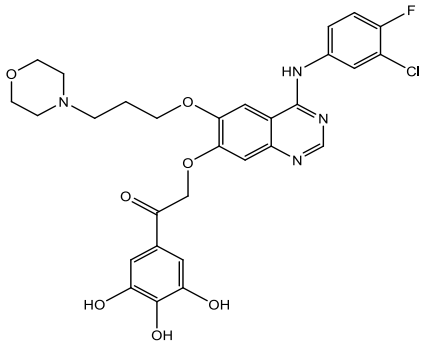
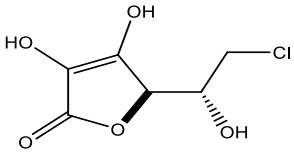
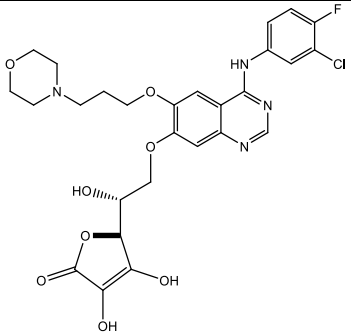
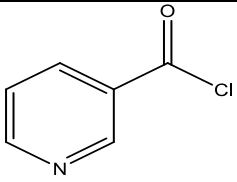
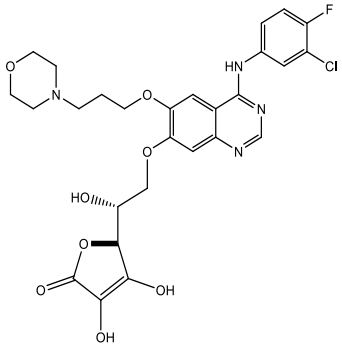
According to the literature survey, we decided to synthesise some anticancer derivatives which clubbed with Gefitinib drug and formed a prodrug [24]. We formed Gefitinib prodrug by using some schemes which are listed below.

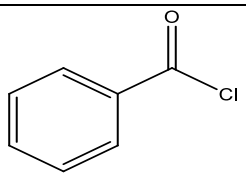
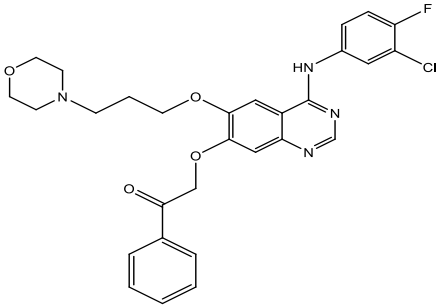
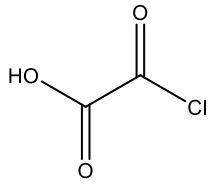
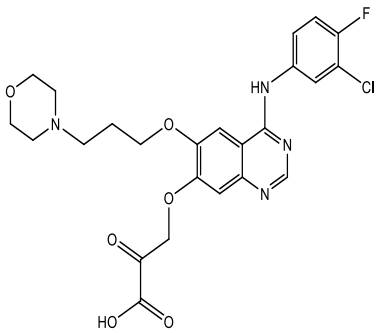
2.1. Reaction Scheme:

Antioxidants and thionyl chloride were utilised to create various derivatives in step 1.

Sr. No.	Antioxidants	Derivatives
1.	 Gallic acid	 Gallic acid chloride (1)
2.	 Ascorbic acid	 Ascorbic acid chloride (2)
3.	 Nicotinic acid	 Nicotinic acid chloride (3)
4.	 Benzoic acid	 Benzoic acid chloride (4)
5.	 oxalic acid	 2-chloro-2-oxoacetic acid (5)

The following steps describe the second. In the presence of the solvent methanol, the drug API (Gefitinib) was combined with a few anticancer derivatives to produce the finished product [25].

Sr. No.	Anticancer Derivatives	Final Products
1.	 Gallic acid chloride (1)	 2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy)quinazolin-7-yloxy)-1-(3,4,5-trihydroxyphenyl)ethanone (6a)
2.	 Ascorbic acid chloride (2)	 (*S*)-5-((*R*)-2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy)quinazolin-7-yloxy)-1-hydroxyethyl)-3,4-dihydroxyfuran-2(5*H*)-one (6b)
3.	 Nicotinic acid chloride (3)	 (*S*)-5-((*R*)-2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy)quinazolin-7-yloxy)-1-hydroxyethyl)-3,4-dihydroxyfuran-2(5*H*)-one (6c)

4.	 Benzoic acid chloride (4)	 2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy)quinazolin-7-yloxy)-1-phenylethanone (6d)
5.	 2-chloro-2-oxoacetic acid (5)	 3-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy)quinazolin-7-yloxy)-2-oxopropanoic acid (6e)

The five derivatives are formed and then these are combined with the anticancer drug Gefitinib to make five anticancer prodrugs of Gefitinib to increase Gefitinib solubility.

- The five compounds of gefitinib prodrugs are made into five tablet formulations by using the direct compression method [25].
- For all five tablet formulations, we performed some individual stability tests like
- Dissolution tests,
- Disintegration tests,
- Friability tests,
- and Hardness tests.
- Which shows the stability of the gefitinib prodrug is increase as compared to the gefitinib drug.

One of the most important strategies for addressing the medical, pharmacokinetic, and pharmacodynamic issues that contribute to the oral solubility of anticancer medications is the modification of these medications into their prodrugs [26].

Gefitinib is an innovative class of prodrugs that enhances oral absorption of anticancer medications by modulating P-glycoprotein, changing the permeability of the gastrointestinal membrane, and transporter-mediated absorption [27].

3. EXPERIMENTAL WORK:

3.1. Materials and Methods

3.1.1. Reagents and Solvents:

Chemicals of LR grade, purchased from spectrochem and loba chem, were used in the synthesis. Before to use in various reactions, all of the solvents employed for the reaction were purified and of LR grade [28]. To record the reaction, pre-coated (Merck 60F 254) plates were used for thin layer chromatography. Petroleum ether and ethyl acetate were utilised as the solvent system for generating the chromatogram in different ratios. Utilizing UV chambers to see TLC spots.

3.1.2. Chemical required:

Gallic acid, Ascorbic acid, Benzoic acid, Nicotinic acid, Oxalic acid, Thionyl chloride, API of Gefitinib, Lactose, Micro-crystalline cellulose, Povidone, Sodium lauryl sulphate, Croscarmellose sodium, Magnesium sterate.

3.1.3. Solvent Required:

Methanol, acetone, Ethanol, Distt. Water, Conc. HCl.

3.1.4. Equipment used:

The compound's identification and characterization were carried out using the capillary m ethod to follow the melting point on a melting point instrument[29]. On a Bruker alpha-E FTIR-ATR,

all the IR spectra of the synthetic compounds were captured. At SAIF, Punjab University, Chandigarh, 1HNMR spectra were captured using a Bruker Avance Neo (500MHz) NM R spectrometer and DMSO as the solvent. Methanol is used as a solvent in a mass spectro meter at Punjab University in Chandigarh.

3.2. Reaction Scheme (Step – 1)

3.2.1. Synthesis of 3,4,5-trihydroxybenzoyl chloride (1)

3.2.1.1. General Reaction:

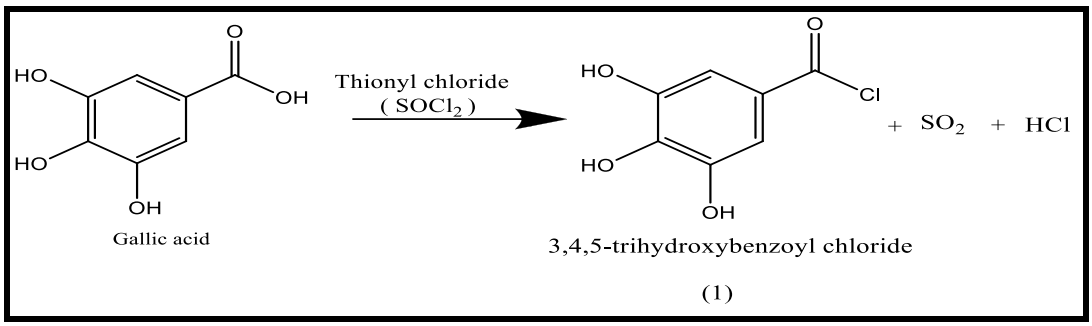


Figure 3.1: Synthesis of 3,4,5-trihydrobenzoyl chloride

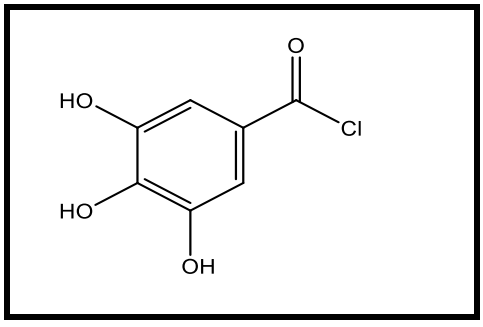
3.2.1.2. General Procedure:

Take 1.7 g (0.1 mol) of gallic acid in a round-bottom volumetric flask and add it to 10 ml of thionyl chloride ($SOCl_2$) dropwise in the reaction. The reaction was refluxed with the condenser in a water bath for 4 hours. The reaction mixture was cooled with ice and kept at room temperature for the night. After that, sulphur dioxide (SO_2) and hydrochloric acid (HCl) were evaporated. As a result, the dry powder is formed as a product (1).

Table: 3.1. Various reagents used for synthesis of compound (1)

Sr. No.	Chemical Used	Moles (M)	Molecular weight (g/mol)	Quality taken
1.	Gallic acid	0.01	170.12	1.7 g
2.	Thionyl chloride	-	118.97	10 ml

3.2.1.3. Observations of 3,4,5-trihydrobenzoyl chloride (1)



Yield	85.5%
R_f value	0.75
Melting point	336.43^oC
Solvent system	Chloroform: Ethanol (9.5:0.5)

for TLC

Molecular formula	$C_7H_5ClO_4$
Molecular Weight	188.57g/mol
State	Powder
Color	Grey

3.2.2. Synthesis of (*R*)-5-((*R*)-2-chloro-1-hydroxyethyl)-3,4-dihydroxyfuran-2(5*H*)-one (2)

3.2.2.1. General Reaction:

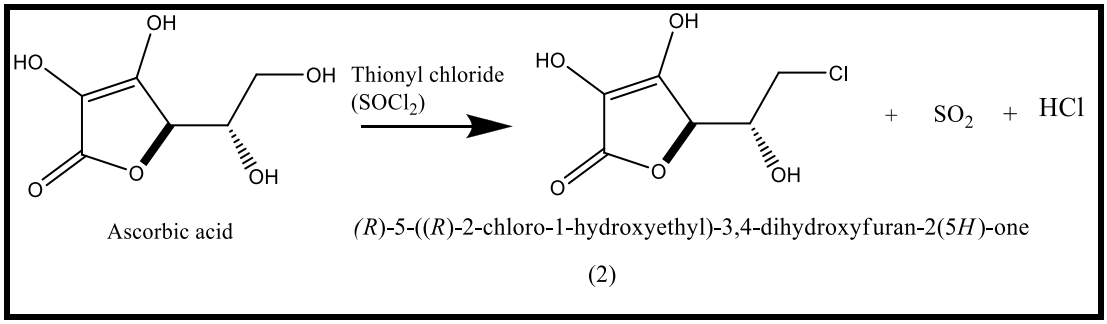


Figure 3.2: Synthesis of (*R*)-5-((*R*)-2-chloro-1-hydroxyethyl)-3,4-dihydroxyfuran-2(5*H*)-one

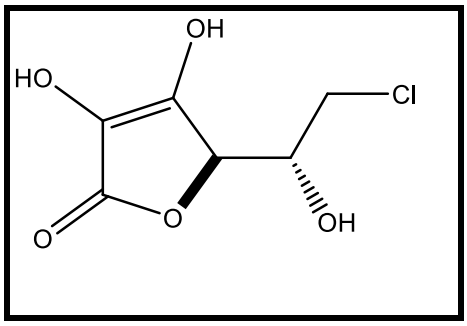
3.2.2.2 General Procedure:

Take 1.76 g (0.1 mol) of ascorbic acid in a round-bottom volumetric flask and add it to 10 ml of thionyl chloride ($SOCl_2$) dropwise in the reaction. The reaction was refluxed with the condenser in a water-bath for 4 hours. The reaction mixture was cooled with ice and kept at room temperature for the night. After that, sulphur dioxide (SO_2) and hydrochloric acid (HCl) were evaporated. As a result, the dry powder is formed as a product (2).

Table: 3.2. Various reagents used for synthesis of compound (2)

Sr. No.	Chemical Used	Moles (M)	Molecular weight (g/mol)	Quality taken
1.	Ascorbic acid	0.01	176.12	1.76 g
2.	Thionyl chloride	-	118.97	10 ml

3.2.2.3. Observation of (*R*)-5-((*R*)-2-chloro-1-hydroxyethyl)-3,4-dihydroxyfuran-2(5*H*)-one (2)



Yield	68.8%
R_f value	0.55
Melting point	167.18^{o}C
Solvent system for TLC	Chloroform: Ethanol (9.5:0.5)
Molecular formula	$C_6H_8O_6$
Molecular Weight	194.57g/mol
State	Powder
Colour	Rust Brown

3.2.3. Synthesis of nicotinoyl chloride

3.2.3.1. General Reaction:

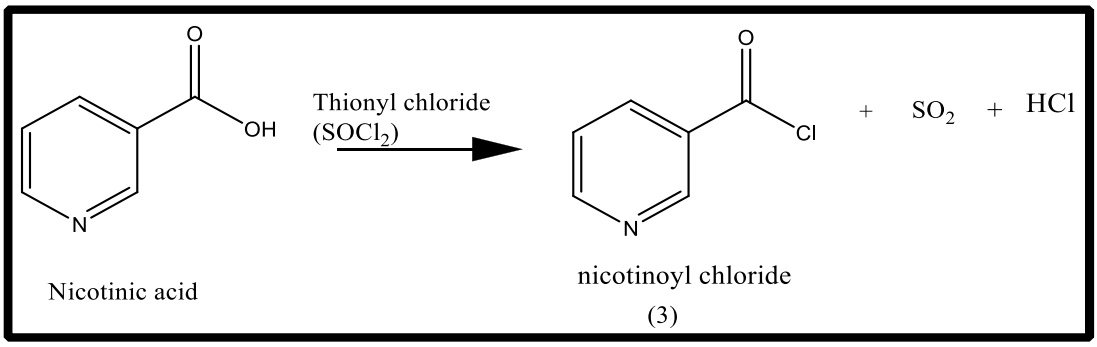


Figure:3.3 Synthesis of nicotinoyl chloride

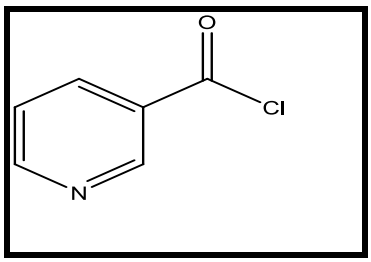
3.2.3.2 General Procedure

Take 1.23 g (0.1 mol) of nicotinic acid in a round-bottom volumetric flask and add it to 10 ml of thionyl chloride ($SOCl_2$) dropwise in the reaction. The reaction was refluxed with the condenser in a water-bath for 4 hours. The reaction mixture was cooled with ice and kept at room temperature for the night. After that, sulphur dioxide (SO_2) and hydrochloric acid (HCl) were evaporated. As a result, the dry powder is formed as a product (3).

Table: 3.3. Various reagents used for synthesis of compound (3)

Sr. No.	Chemical Used	Moles (M)	Molecular weight (g/mol)	Quality taken
1.	Nicotinic acid	0.01	123.1094	1.23 g
2.	Thionyl chloride	-	118.97	10 ml

3.2.3.3. Observation of nicotinoyl chloride (3)



Yield 78.62%

R_f value 0.25

Melting point 61.54^oC

Solvent system for TLC Chloroform: Ethanol (9.5:0.5)

Molecular formula C_6H_4ClNO

Molecular Weight 141.56g/mol

State Powder

Colour whitish

3.2.4. Synthesis of benzoyl chloride

3.2.4.1. General Reaction:

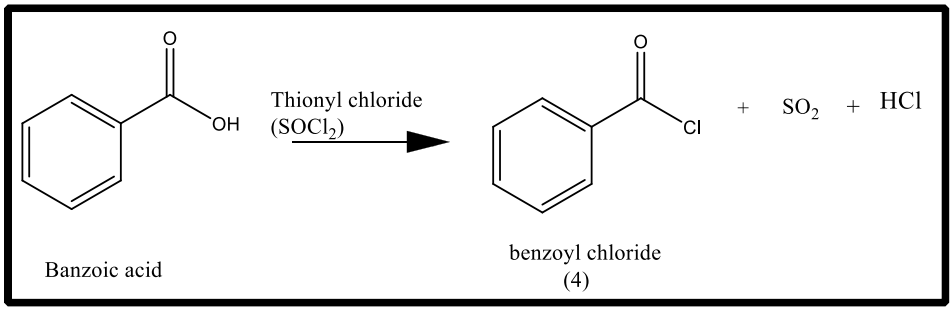


Figure:3.4 Synthesis of benzoyl chloride

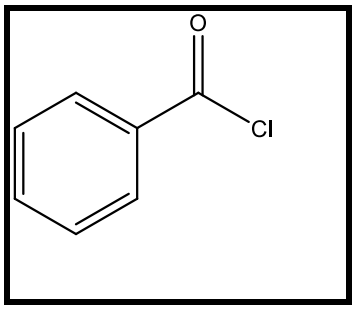
3.2.4.2 General Procedure

Take 1.22 g (0.1mol) of benzoic acid in a round-bottom volumetric flask and add it to 10ml of thionyl chloride ($SOCl_2$) dropwise in the reaction. The reaction was refluxed with the condenser in a water-bath for 4 hours. The reaction mixture was cooled with ice and kept at room temperature for the night. After that, sulphur dioxide (SO_2) and hydrochloric acid (HCl) were evaporated. As a result, the dry powder is formed as a product (4).

Table: 3.4. Various reagents used for synthesis of compound (4)

Sr. No.	Chemical Used	Moles (M)	Molecular weight (g/mol)	Quality taken
1.	Benzoic acid	0.01	122.12	1.22g
2.	Thionyl chloride	-	118.97	10 ml

3.2.4.3. Observation of benzoyl chloride (4)



Yield	80.2%
R_f value	0.78
Melting point	197ºC
Solvent system for TLC	Chloroform: Ethanol (9.5:0.5)
Molecular formula	C_7H_5ClO
Molecular Weight	140.57g/mol
State	Powder
Color	Brown

3.2.5. Synthesis of 2-chloro-2-oxoacetic acid (5)

3.2.5.1. General Reaction:

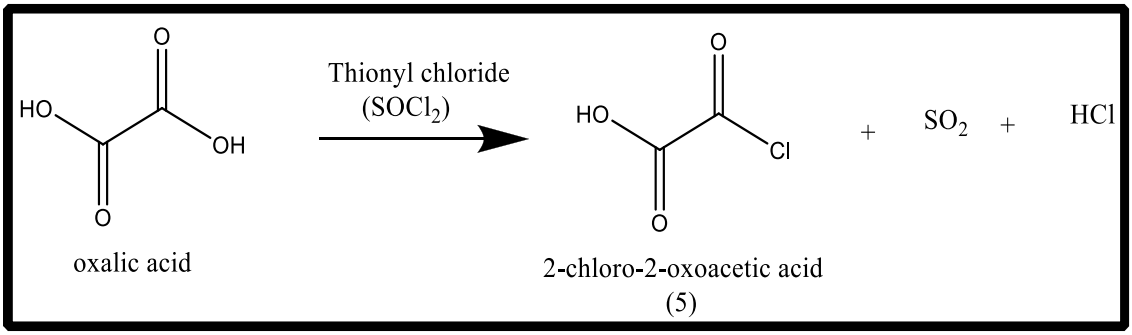


Figure:3.5 Synthesis of 2-chloro-2-oxoacetic acid

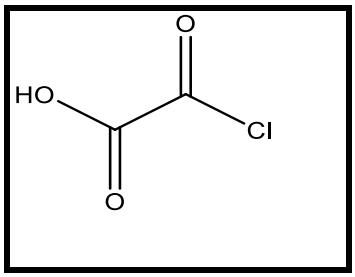
3.2.5.2 General Procedure

Take 0.9g (0.1 mol) of oxalic acid in a round-bottom volumetric flask and add it to 10 ml of thionyl chloride ($SOCl_2$) dropwise in the reaction. The reaction was refluxed with the condenser in a water-bath for 4 hours. The reaction mixture was cooled with ice and kept at room temperature for the night. After that, sulphur dioxide (SO_2) and hydrochloric acid (HCl) were evaporated. As a result, the dry powder is formed as a product (5).

Table: 3.5. Various reagents used for synthesis of compound (5)

Sr. No.	Chemical Used	Moles (M)	Molecular weight (g/mol)	Quality taken
1.	Oxalic acid	0.01	90.03	0.9 g
2.	Thionyl chloride	-	118.97	10 ml

3.2.5.3. Observation of 2-chloro-2-oxoacetic acid (5)



Yield 72.56%

R_f value 0.63

Melting point 244^oC

Solvent system Chloroform: Ethanol (9.5:0.5)

for TLC

Molecular formula 108.48g/ml

Molecular Weight C_2HClO_3

State Powder

Colour White

3.3. Reaction scheme (Step - 2)

3.3.1. Synthesis of 2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-1-(3,4,5-trihydroxyphenyl) ethenone (6a)

3.3.1.1. General Reaction:

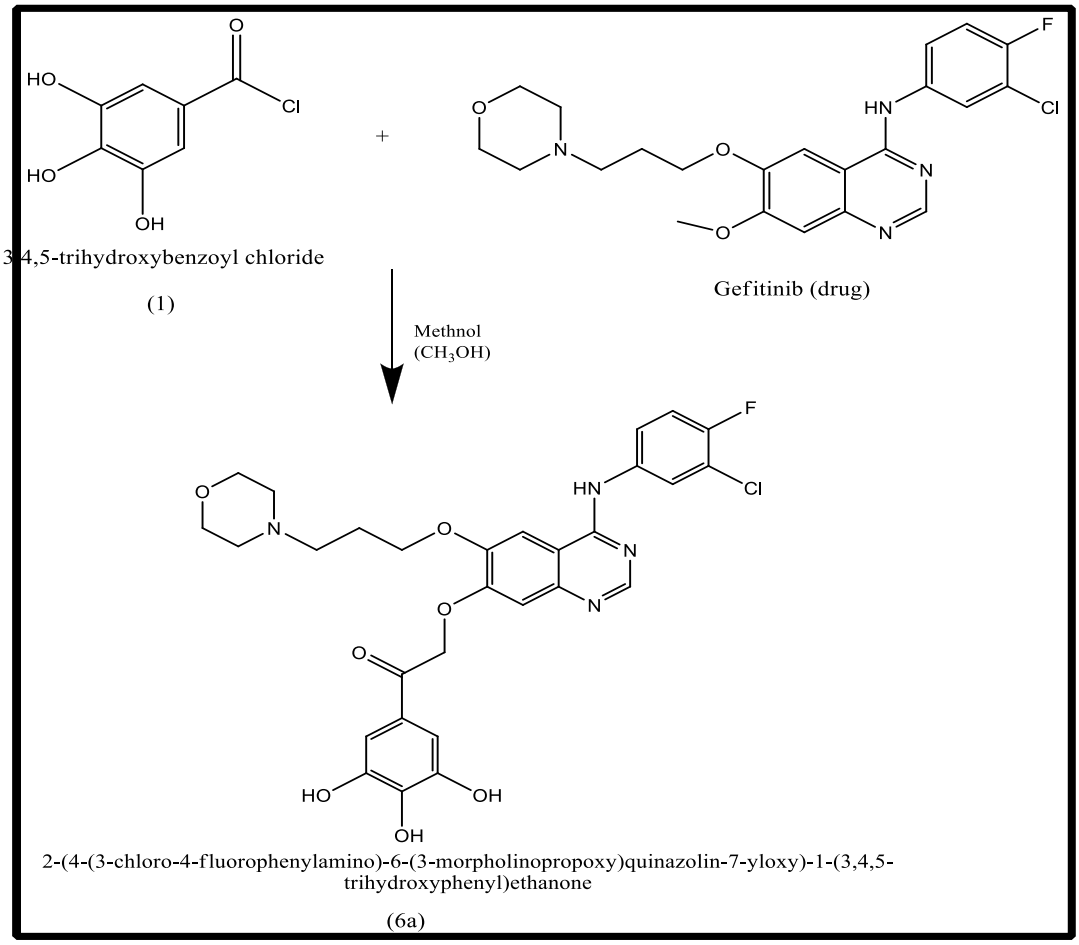


Figure 3.6. Synthesis of 2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-1-(3,4,5-trihydroxyphenyl) ethenone

3.3.1.2. General Procedure:

The mixture of compound (1) 1.88 g (0.01 mol) and API of Gefitinib drug weighed 4.46 g (0.01 mol) in a round-bottom volumetric flask and was soluble in 10 ml of methanol (CH_3OH). Then the reaction was refluxed with the condenser in a water-bath for 1 hour. The reaction mixture was cooled with ice and kept at room temperature for the night. As a result, the dry powder is formed as a final product (6a).

Table: 3.6. Various reagents used synthesis of compound (6a)

Sr. No.	Chemical Used	Moles (M)	Molecular weight (g/mol)	Quality taken
1.	3,4,5-trihydrobenzoyl chloride	0.01	188.57	1.88 g
2.	API (Gefitinib)	0.01	446.902	4.46 g
3.	Methanol	-	-	10 ml

Similarly

3.3.2. Synthesis and Observation of (S)-5-((R)-2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-1-hydroxyethyl)-3,4-dihydroxyfuran-2(5H)-one (6b)

3.3.2.1. General Reaction:

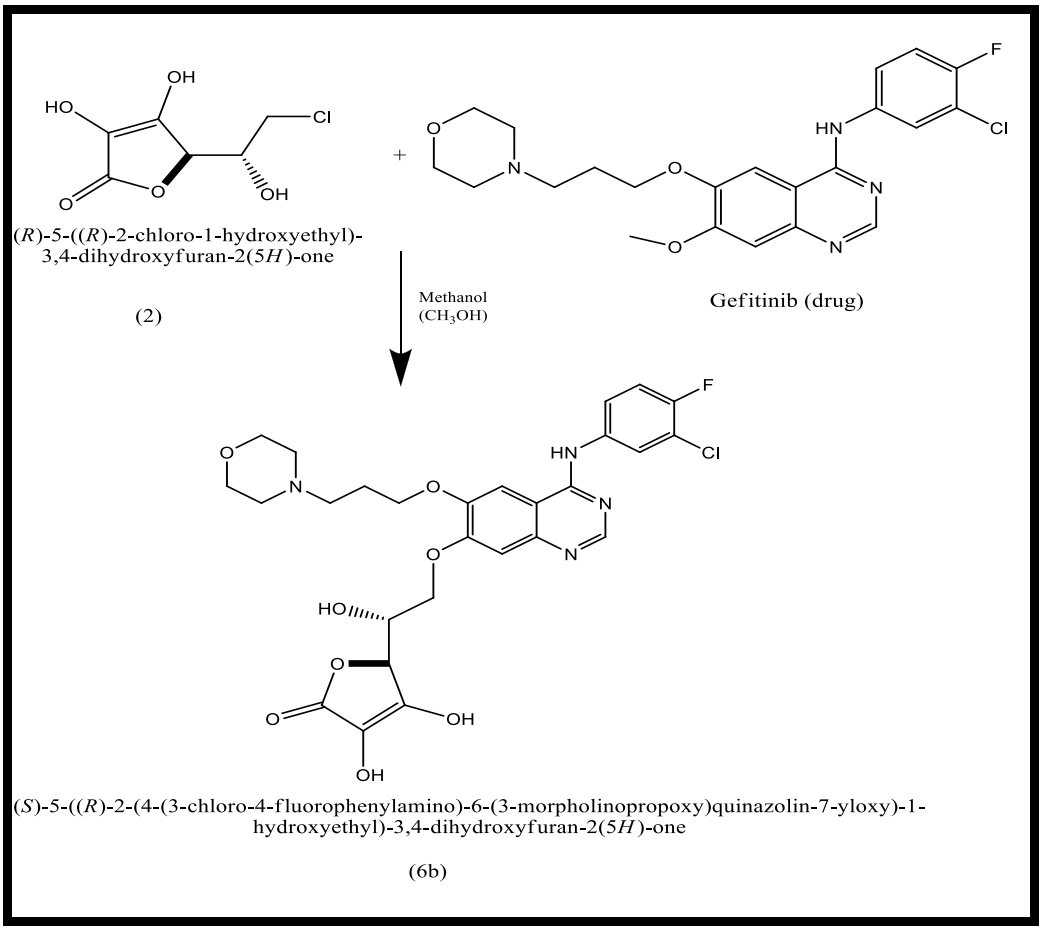


Figure:3.7. Synthesis and Observation of (*S*)-5-((*R*)-2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-1-hydroxyethyl)-3,4-dihydroxyfuran-2(5*H*)-one

3.3.3. Synthesis of 2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-1-(pyridin-3-yl) ethenone (6c)

3.3.3.1. General Reaction:

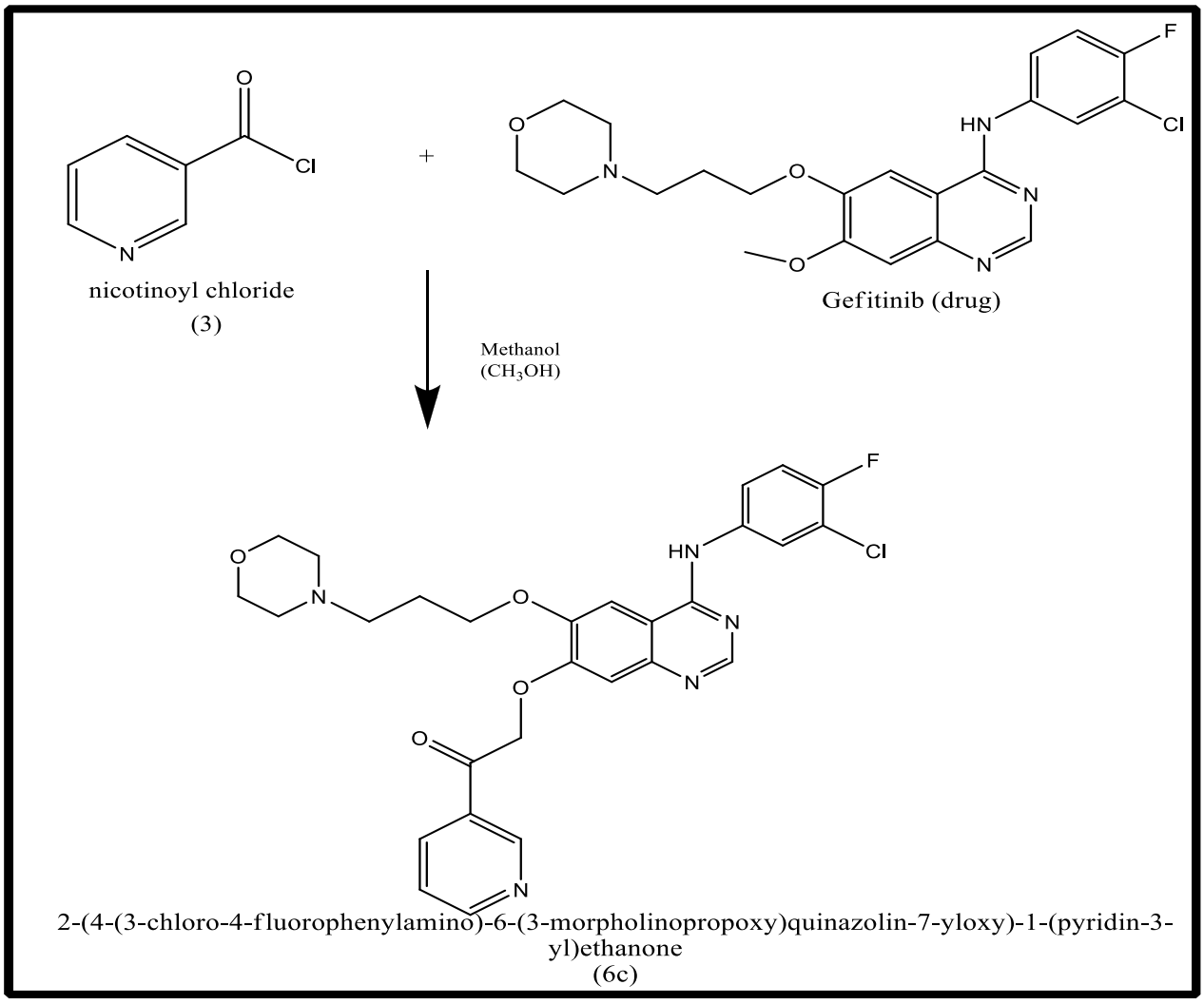


Figure:3.8. Synthesis of 2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-1-(pyridin-3-yl) ethenone

3.3.4. Synthesis of 2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-1-phenylethanone (6d)

3.3.4.1. General Reaction:

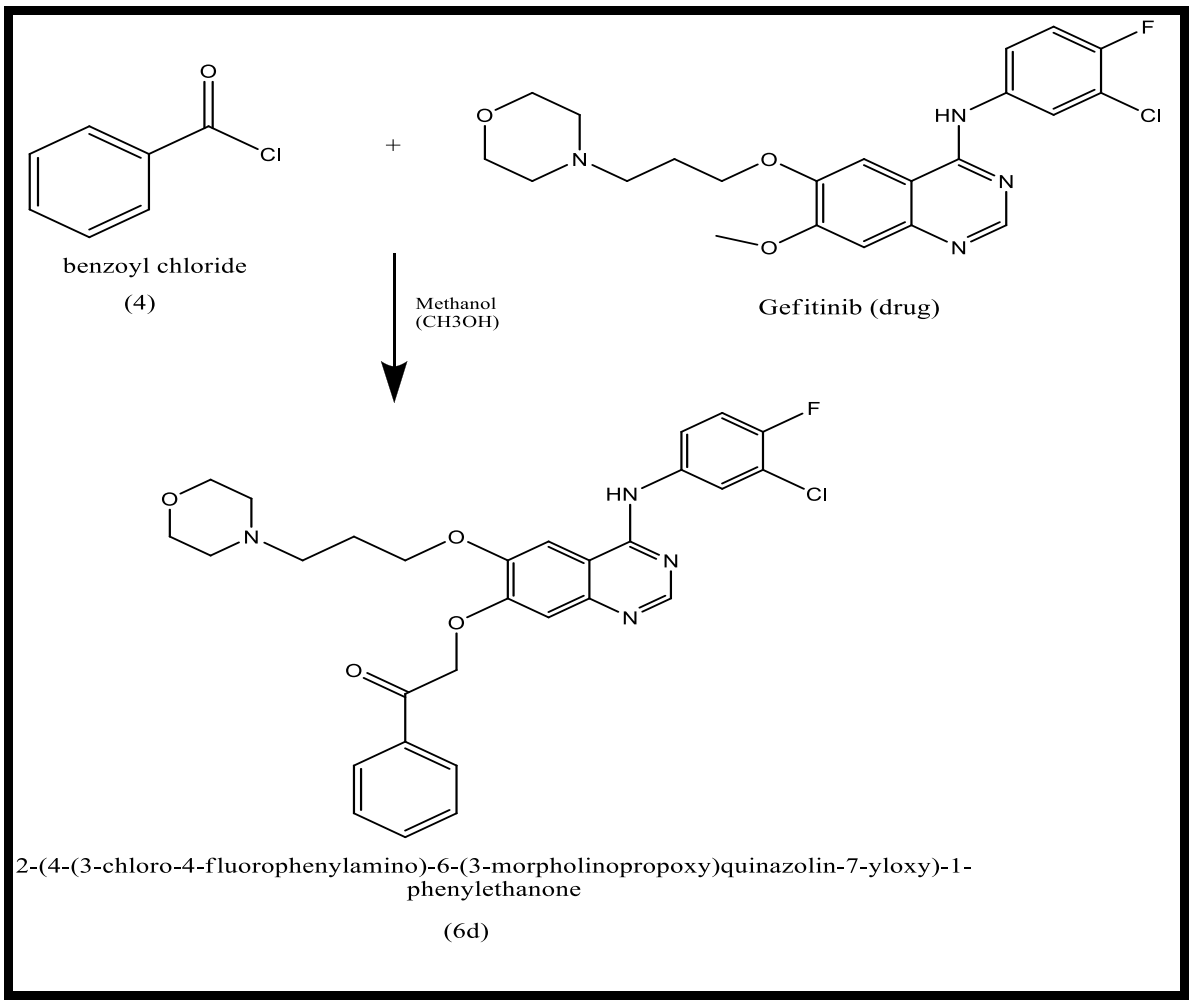


Figure:3.9. Synthesis of 2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-1-phenylethanone

3.3.5. Synthesis of 3-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-2-oxopropanoic acid (6e)

3.3.5.1. General Reaction:

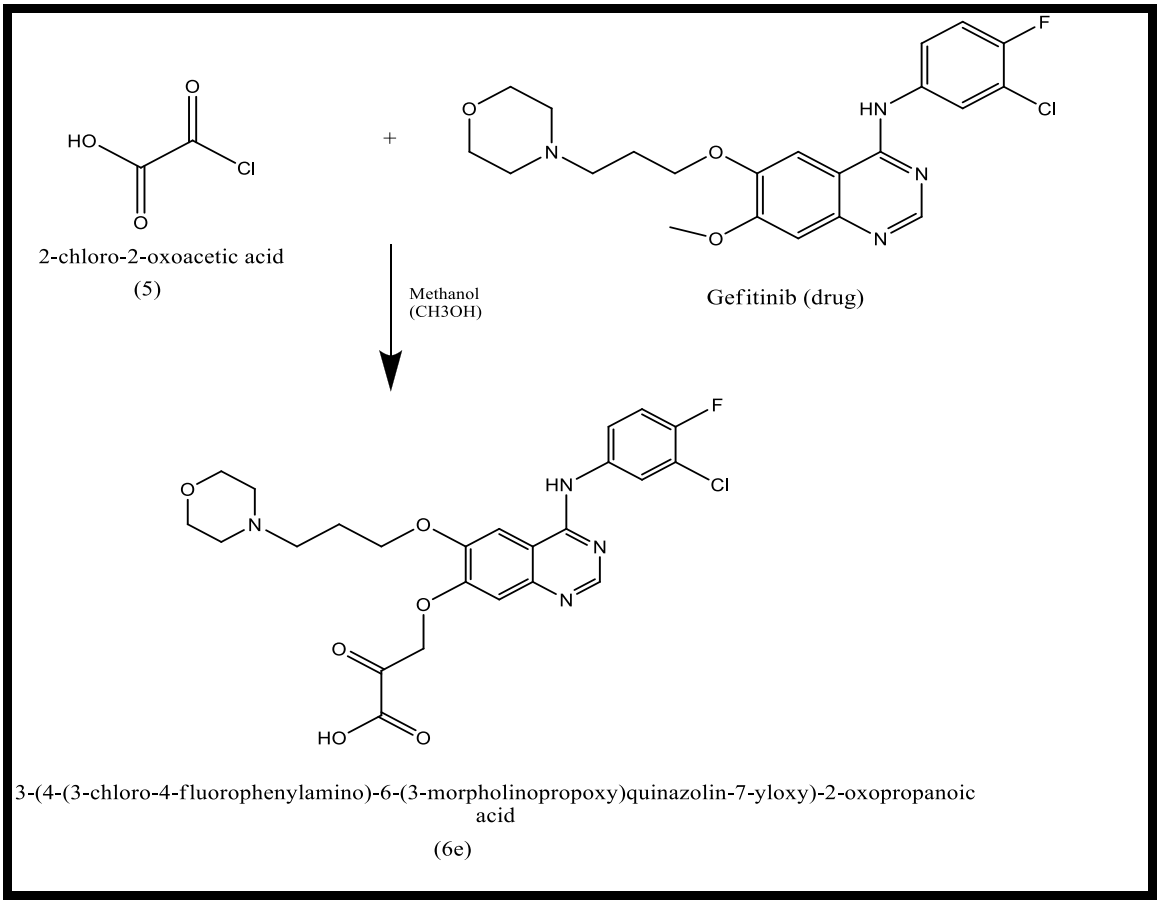


Figure:3.10. Synthesis of 3-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-2-oxopropanoic acid

3.3 Formulations of Tablets:

- The five compounds of gefitinib prodrugs are made into five tablet formulations by using the direct compression method.
- For all five tablet formulations, we performed some individual stability tests like

- Dissolution tests,
- Disintegration tests,
- Friability tests,
- and Hardness tests.

which shows the stability of the gefitinib prodrug is increasing as compared to the gefitinib drug.

4. RESULTS AND DISCUSSION:

As per the proposed reaction scheme, the synthesis of some anticancer derivatives and clubbed with Gefitinib drug and then formed Gefitinib Prodrug (6a-e) was carried out.

- Thionyl chloride was used in the first step, good yields were obtained for 3,4,5-trihydrobenzoyl chloride (1), (*R*)-5-((*R*)-2-chloro-1-hydroxyethyl)-3,4-dihydroxyfuran-2(5*H*)-one (2), nicotinoyl chloride (3), benzoyl chloride (4), and 2-chloro-2-oxoacetic acid (5).
- In the next step, these were then combined with the API Gefitinib drug to produce 2-(4-(3-chloro-4-fluorophenylamino) -6- (3-morpholinopropoxy) quinazolin-7-yloxy) -1- (3,4,5-trihydroxyphenyl) ethenone (6a), (*S*) -5- ((*R*) -2- (4-(3-chloro-4-fluorophenylamino) -6- (3-morpholinopropoxy) quinazolin-7-yloxy)-1-hydroxyethyl)-3, 4-dihydroxyfuran-2(5*H*)-one (6b), 2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy) 1-(pyridin-3-yl) ethenone (6c), 2-(4-(3-chloro-4-fluorophenylamino) -6- (3-morpholinopropoxy) quinazolin-7-yloxy) quinazolin-7-yloxy) quinazolin-7-yloxy) quinazolin-7-yloxy) quinazolin 1-phenylethanone (6d) and 3-(4-(3-chloro-4-fluorophenylamino) -6- (3-morpholinopropoxy) quinazolin-7-yloxy) -2- oxo propanoic acid (6e) in the presence of the solvent methanol.

The reaction was monitored by thin layer chromatography using solvent system such as chloroform: ethanol. After the completion of the reaction the products were purified by suitable method.

Tablet 4.1: Physical Characteristics of Synthesized Compounds 6(a-e)

Comp. No.	Molecular Formula	Molecular Weight (g)	Melting point (°C)	R_f	Yield (%)
6a	$C_{29}H_{28}ClFN_4O_7$	599.01 g/mol	286 °C	0.58	78%
6b	$C_{27}H_{28}ClFN_4O_8$	590.98 g/mol	220 °C	0.23	62%
6c	$C_{28}H_{27}ClFN_5O_4$	552 g/mol	266 °C	0.52	55%
6d	$C_{29}H_{28}ClFN_4O_4$	551.01 g/mol	258 °C	0.27	44.94%
6e	$C_{24}H_{24}ClFN_4O_6$	518.92 g/mol	216 °C	0.56	55%

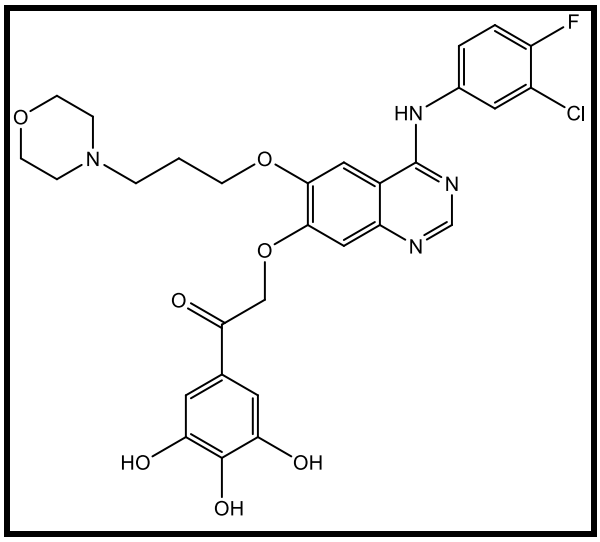
*R_f = Chloroform: Ethanol

All the derivatives were confirmed by various physical properties like state, R_f value, melting point and spectral techniques like IR and ^{1}HNMR.

The brief outcome of the physical characteristics is described in Table 6.1. The melting point was observed in the range of 216-286^{0}C. The R_f values were observed in the range of 0.23-0.58. All the products were obtained in good yields varying from the 44-78%.

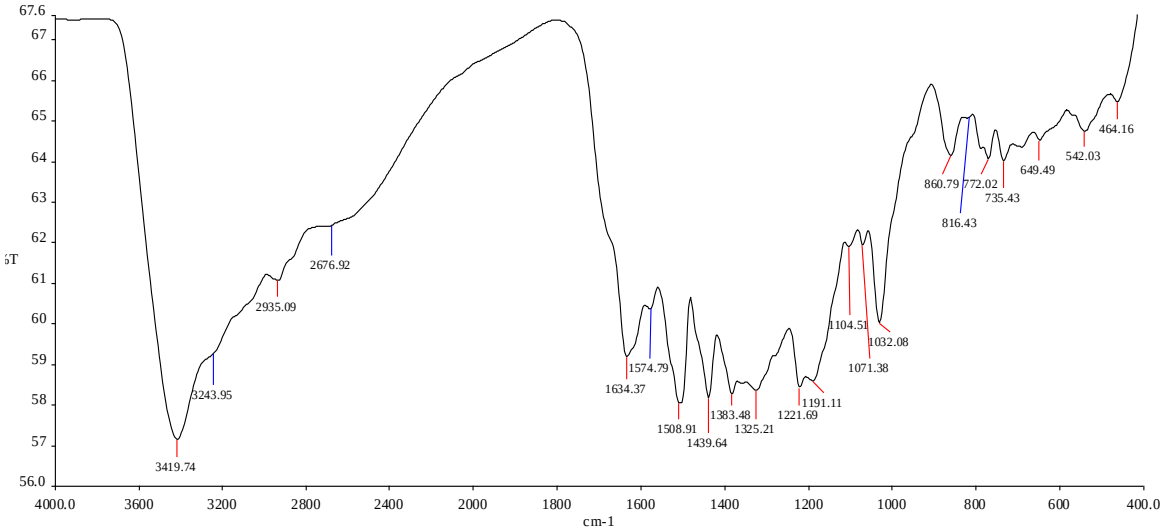
4.1 SPECTRAL CHARACTERISTICS OF THE SYNTHESIZED COMPOUNDS

4.1.1. Spectral characteristics of 2-(4-(3-chloro-4-fluorophenylamino)-6 morpholinopropoxy) quinazolin-7-yloxy)-1-(3,4,5-trihydroxyphenyl) ethenone (6a)



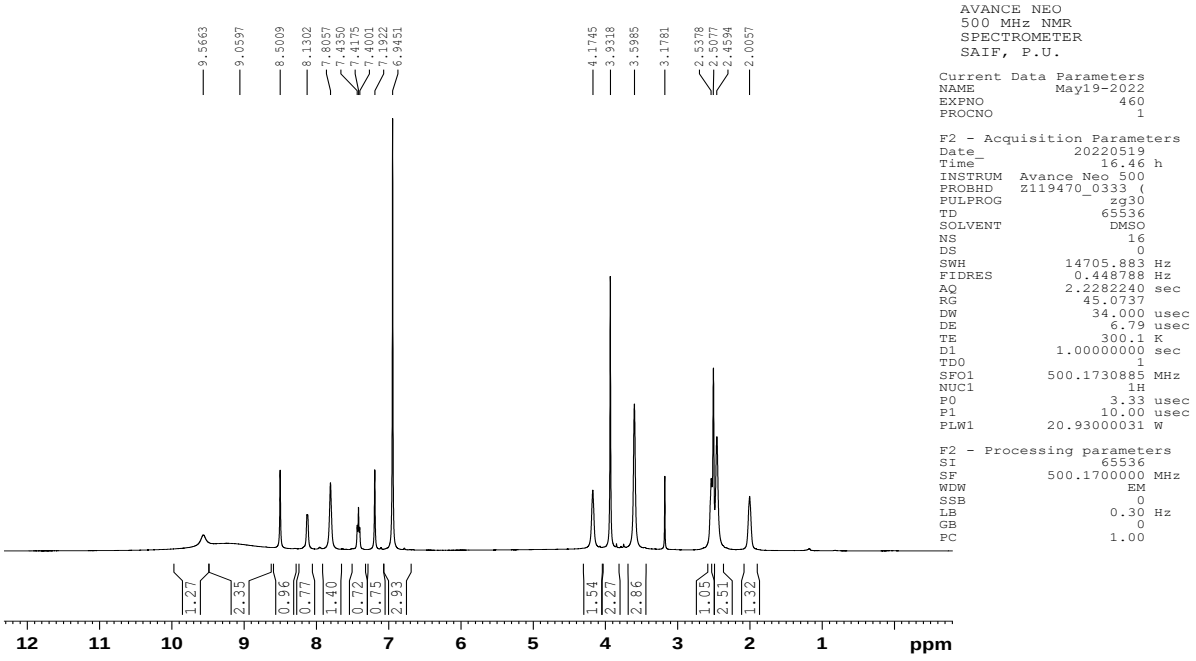
A Brown Solid with Molecular formula $C_{29}H_{28}ClFN_4O_7$ and Molecular Weight 599.01 g/mol yielded 78% with melting point in the range of 286 ^{o}C and R_f value of 0.58.

IR spectra of compound 6a



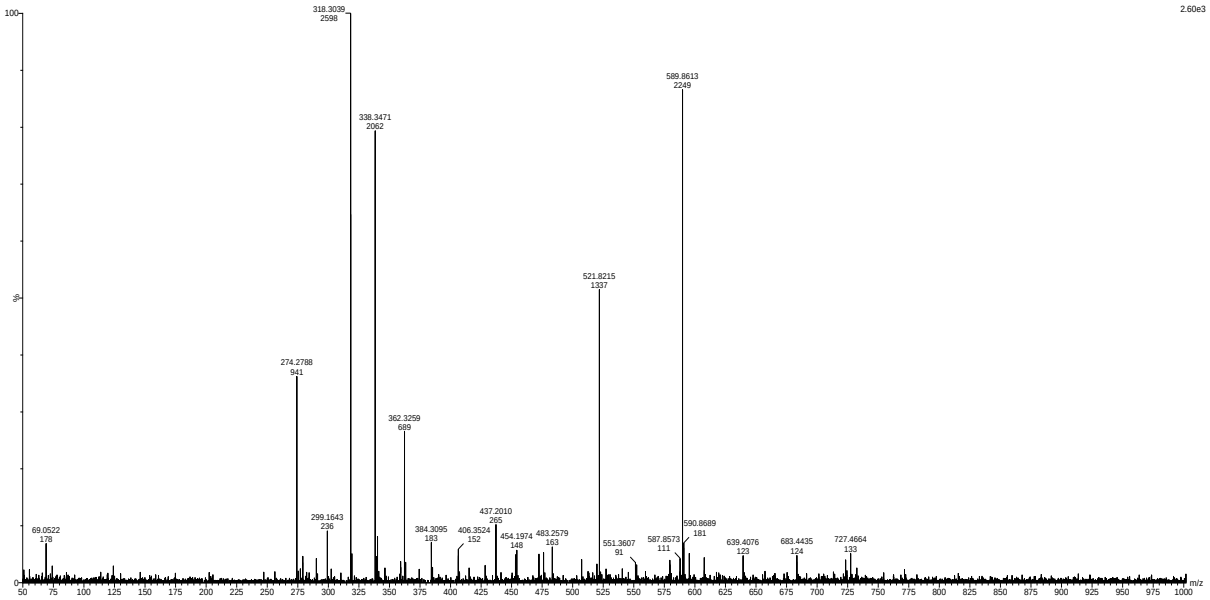
IR (cm^{-1}): The IR spectra of compounds exhibited absorption bond at 3243.95cm^{-1} (Ar-C-H stretch), 1723.55cm^{-1} (Ar-C=O stretch), 1634.37cm^{-1} (Ar-C=N stretch), 1071.38cm^{-1} (Ar-C-N stretch), 1574.79cm^{-1} (Ar-C=C stretch), 1439.64cm^{-1} aromatic (=CH-sp^2 stretch), 2935.09cm^{-1} (Ar-N-H stretch), 1071cm^{-1}(CF stretch).

[1]HNMR spectra of compound 6a



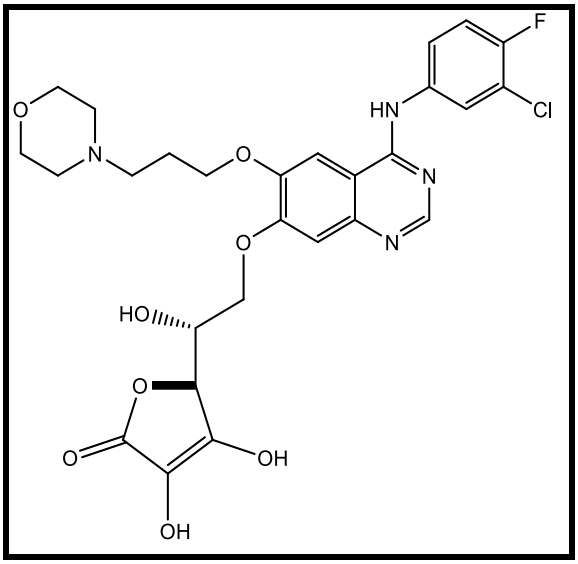
[1]HNMR (DMSO-d_6, 500MHz, δ ppm): 4.0 (s, 1H, NH), 3.65-2.36 (m, Ar-H, CH_2), 5.70, 4.06, 2.46, 1.82 (m, Methylene, CH_2), 5.35 (t, aromatic C-OH), 8.46, 7.41, 7.24 (t, CH, quinazoline), 6.79, 7.16, 6.84, 7.29 (m, CH, benzene).

MS spectra of compound 6a



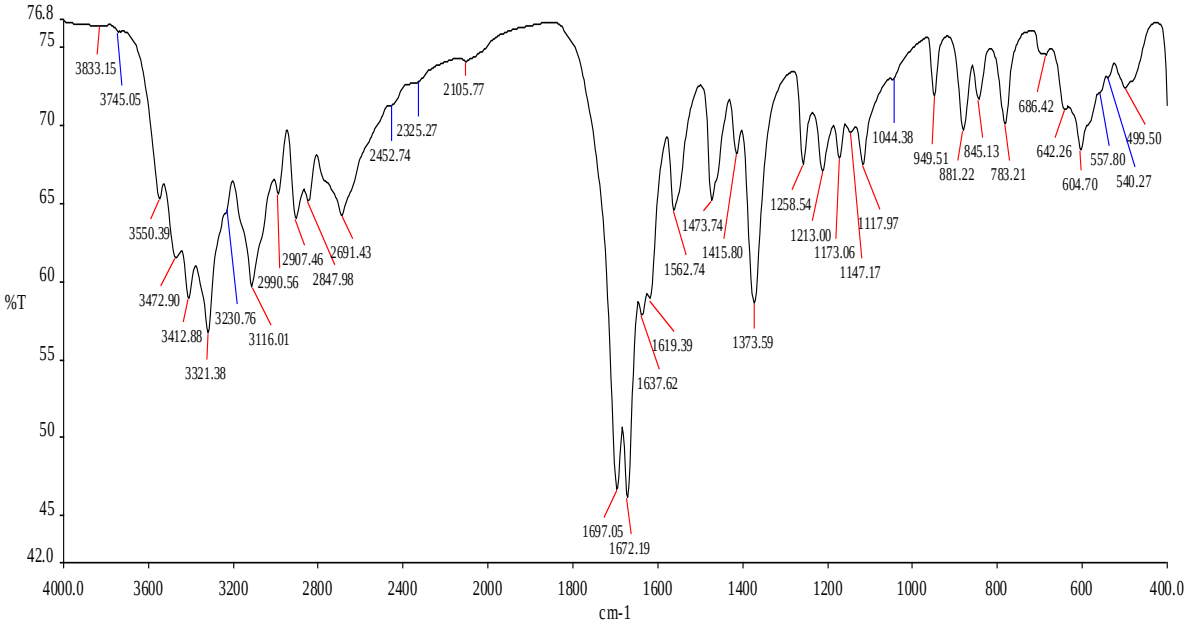
MS (m/z): Actual molecular weight (599.01 g/mol), and we found (589.86 g/mol).

4.1.2. Spectral characteristics of (*S*)-5-((*R*)-2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-1-hydroxyethyl)-3,4-dihydroxyfuran-2(5*H*)-one (6b)



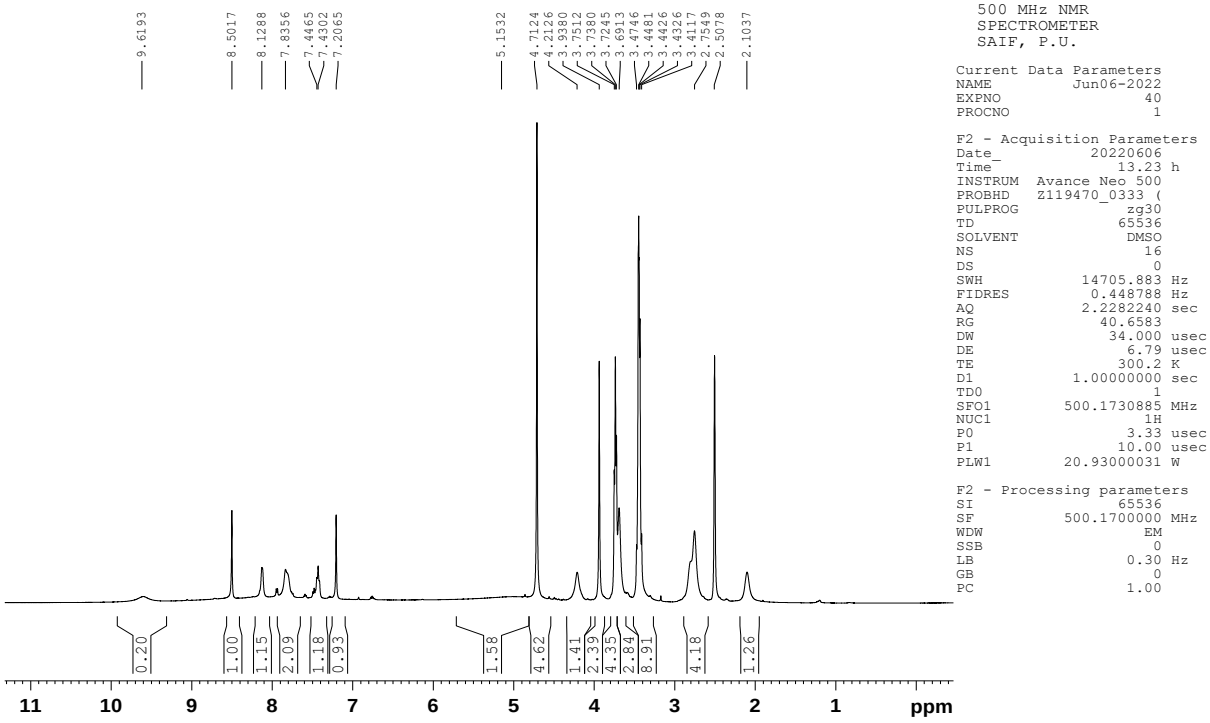
A white Solid with Molecular formula $C_{27}H_{28}ClFN_4O_8$ and Molecular Weight 590.98g/mol yielded 62% with melting point in the range of 220 °C and R_f value of 0.23.

IR spectra of compound 6 b



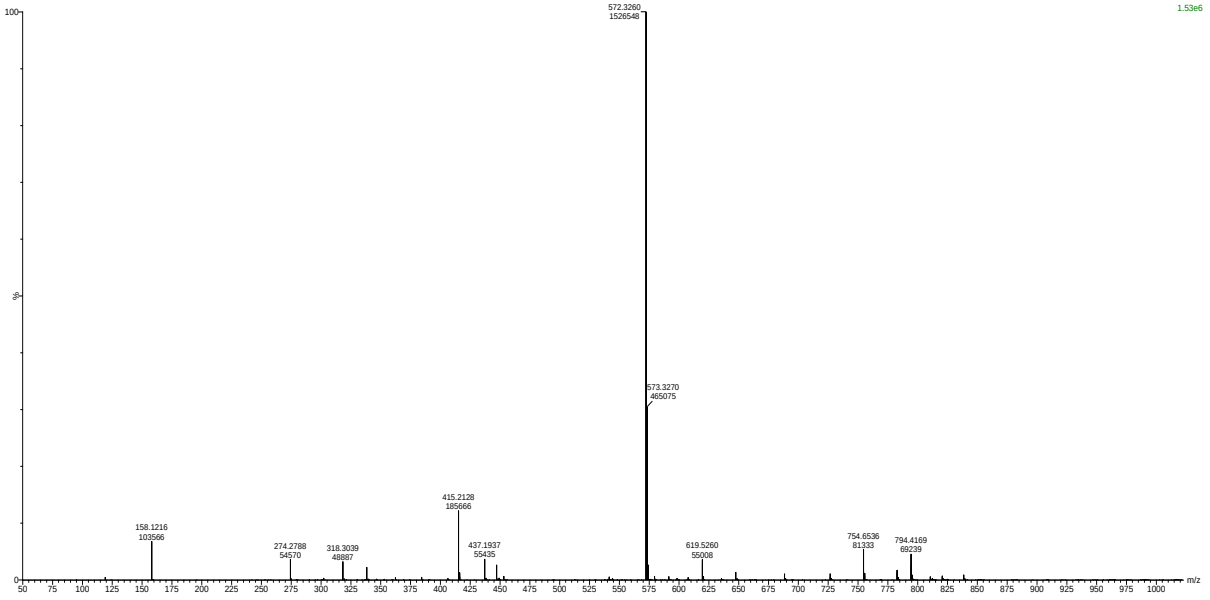
IR (cm^{-1}): The IR spectra of compounds exhibited absorption bond at 3550.39cm^{-1} (Ar-C-H stretch), 1713.55cm^{-1} (Ar-C=O stretch), 1256.74cm^{-1} (C-O stretch), 1614.37cm^{-1} (Ar-C=N stretch), 1173.06 cm^{-1} (Ar-C-N stretch), 1564.79cm^{-1} (Ar-C=C stretch), 1473.74cm^{-1} aromatic (=CH-sp^2 stretch), 2907.46cm^{-1} (Ar-N-H stretch), 1044cm^{-1}(CF stretch).

[1]HNMR spectra of compound 6b



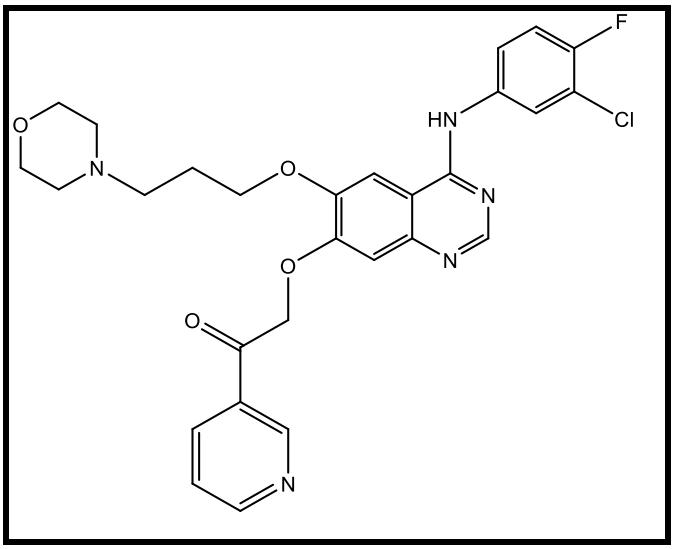
[1]HNMR (DMSO-d_6, 500MHz, δ ppm): 4.0 (s, 1H, NH), 3.65-2.36 (m, Ar-H, CH_2), 4.21, 2.46, 1.82 (t, Methylene, CH_2), 5.35 (t, aromatic C-OH), 8.49, 7.41, 7.24 (t, CH, quinazoline), 5.0 (s, CH, furanon), 6.79, 7.16, 6.84, 7.29 (m, CH, benzene), 4.35 (s, CH, methine).

MS spectra of compound 6b



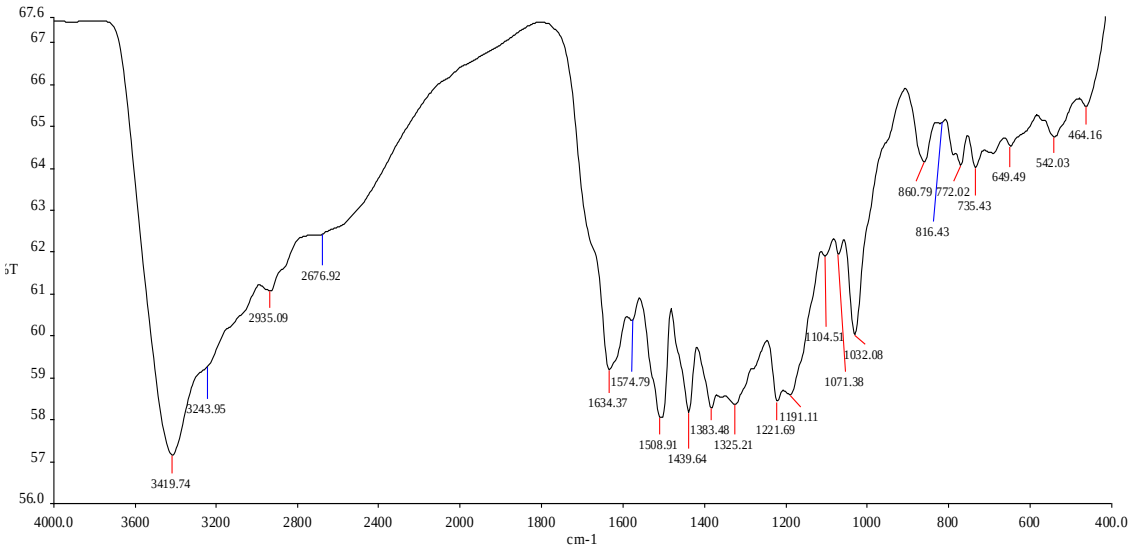
MS (m/z): Actual molecular weight (590.89 g/mol), and we found (572.32 g/mol).

4.1.3. Spectral characteristics of 2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-1-(pyridin-3-yl) ethenone (6c).



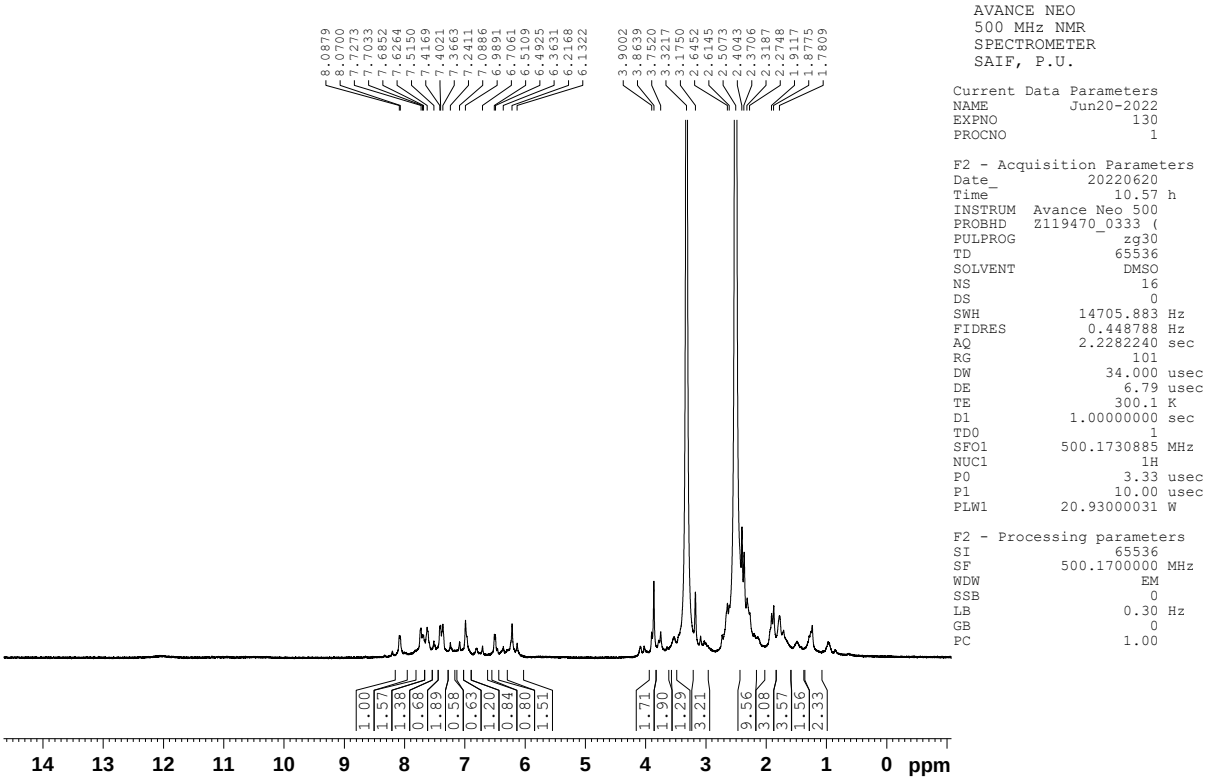
A brownish Solid with Molecular formula $C_{28}H_{27}ClFN_5O_4$ and Molecular Weight 552g/mol yielded 55% with melting point in the range of 266 ºC and R_f value of 0.52.

IR spectra of compound 6c



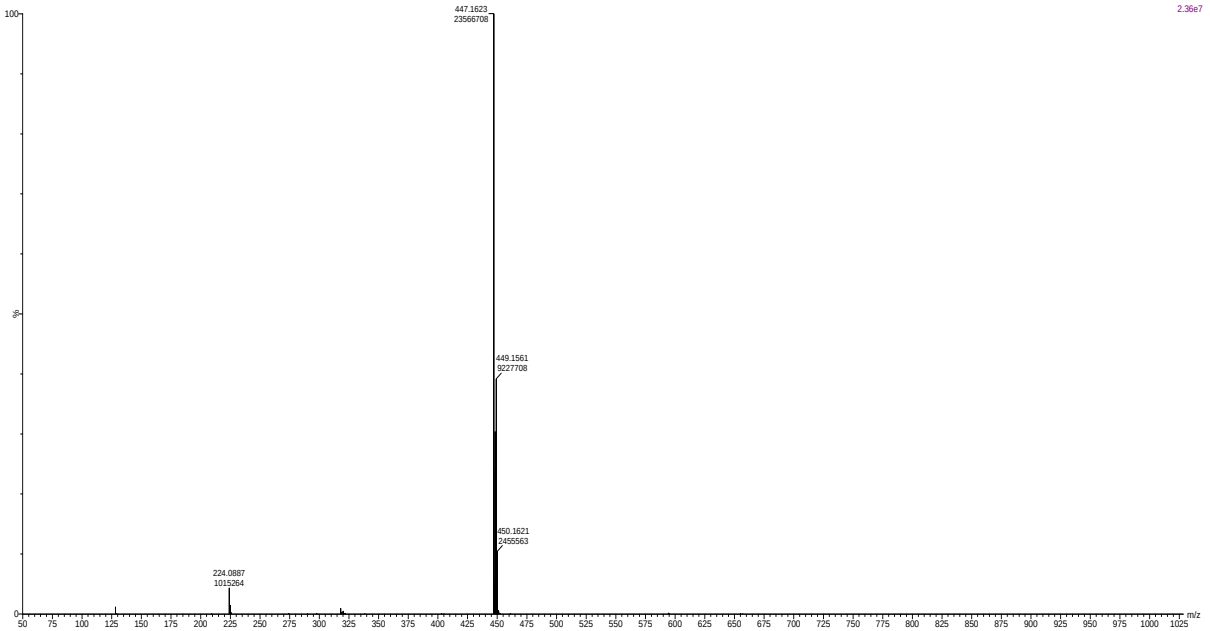
IR (cm^{-1}): The IR spectra of compounds exhibited absorption bond at 3243.95cm^{-1} (Ar-C-H stretch), 1.55cm^{-1} (Ar-C=O stretch), 1634.37cm^{-1} (Ar-C=N stretch), 1071.38cm^{-1} (Ar-C-N stretch), 1574.79cm^{-1} (Ar-C=C stretch), 1439.64cm^{-1} aromatic (=CH-sp^2 stretch), 2935.09cm^{-1} (Ar-N-H stretch).

[1]HNMR spectra of compound 6c



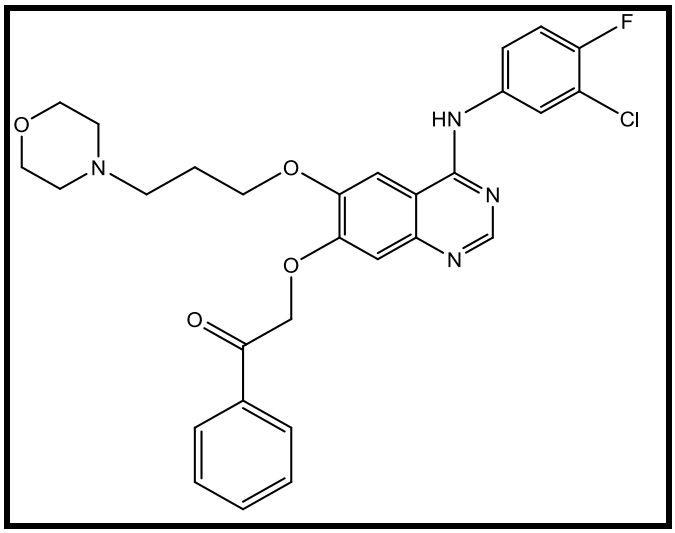
[1]HNMR (DMSO-d_6, 500MHz, δ ppm): 4.0 (s, 1H, NH), 3.65-2.36 (m, Ar-H, CH_2), 4.21, 2.46, 1.82 (t, Methylene, CH_2), 5.35 (t, aromatic C-OH), 8.46, 7.41, 7.24 (t, CH, quinazoline), 6.79-7.29 (m, CH, benzene), 8.82-9.15 (m, CH, pyridine).

MS spectra of compound 6c



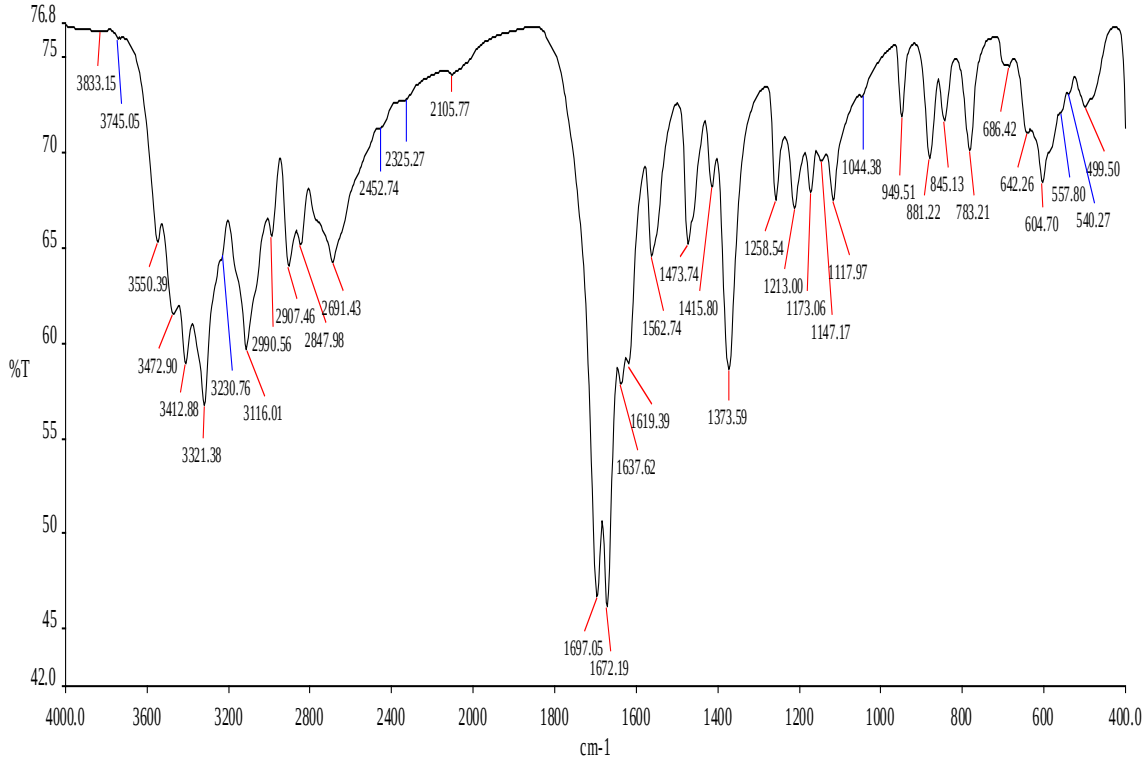
MS (m/z): Actual molecular weight (552 g/mol), and we found (457.32 g/mol).

4.1.4. Spectral characteristics of 2-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-1-phenylethanone (6d)



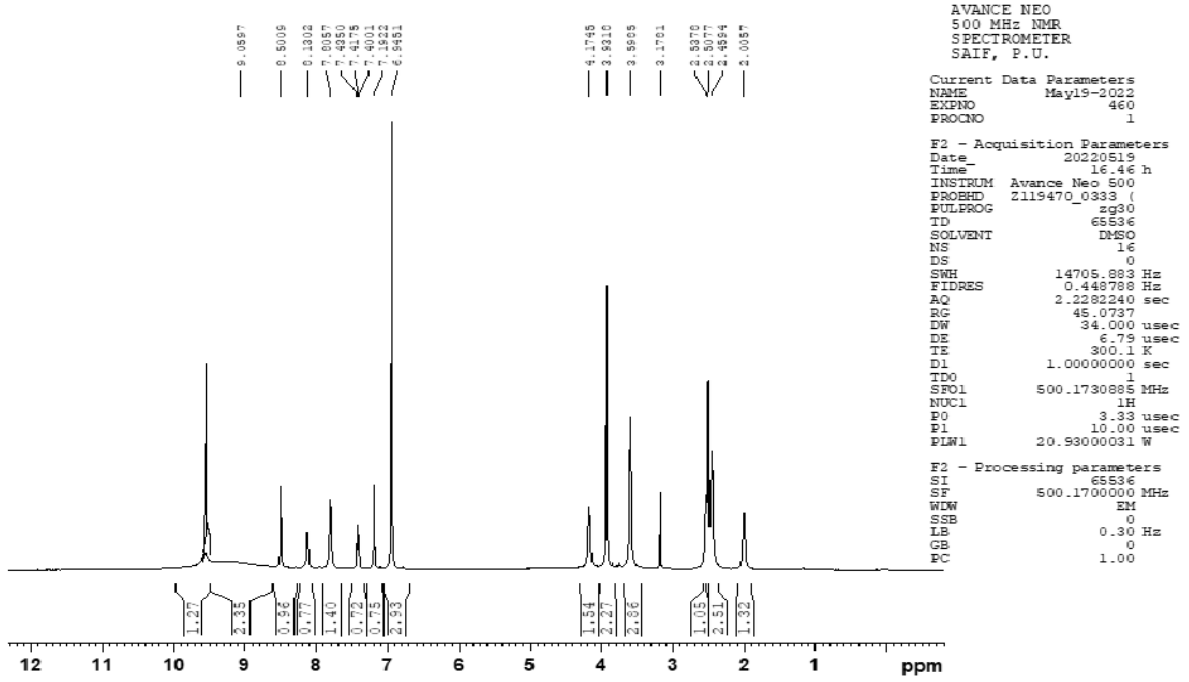
A Sunset Yellow Solid with Molecular formula $C_{29}H_{28}ClFN_4O_4$ and Molecular Weight 551.01g/mol yielded 44.94% with melting point in the range of 258 ºC and R_f value of 0.27.

IR spectra of compound 6d



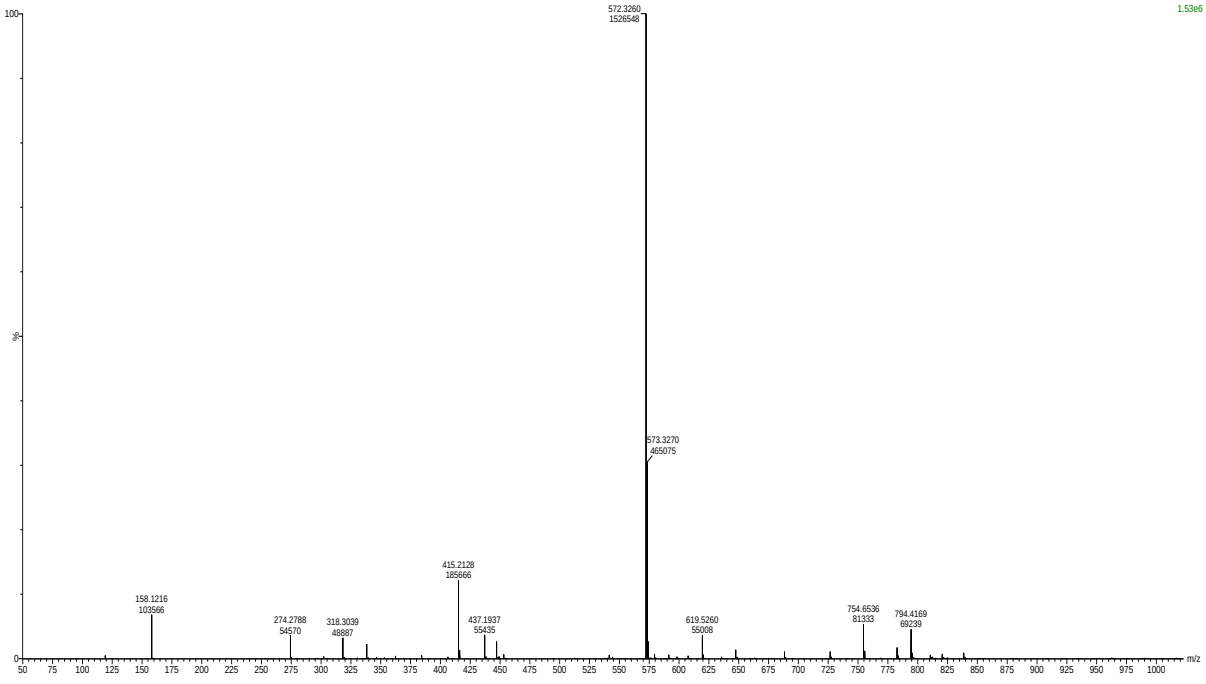
IR (cm^{-1}): The IR spectra of compounds exhibited absorption bond at 3230.90cm^{-1} (Ar-C-H stretch), 1697.05cm^{-1} (Ar-C=O stretch), 1637.62cm^{-1} (Ar-C=N stretch), 1071.38cm^{-1} (Ar-C-N stretch), 1562.79cm^{-1} (Ar-C=C stretch), 1473.64cm^{-1} aromatic (=CH-sp^2 stretch), 2990.56cm^{-1} (Ar-N-H stretch), 1590.55cm^{-1} (benzene).

[1]HNMR spectra of compound 6d



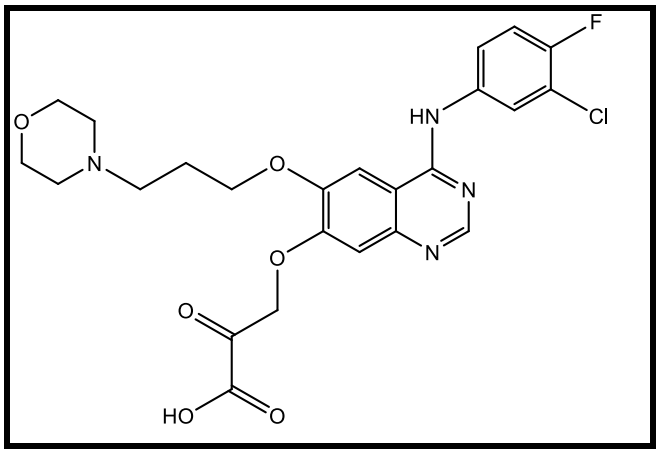
[1]HNMR (DMSO-d_6, 500MHz, δ ppm): 4.0 (s, 1H, NH), 3.65-2.36 (m, Ar-H, CH_2), 4.21, 2.46, 1.82 (t, Methylene, CH_2), 5.35 (t, aromatic C-OH), 8.46, 7.41, 7.24 (t, CH, quinazoline), 6.79-7.29 (m, CH, benzene).

MS spectra of compound 6d



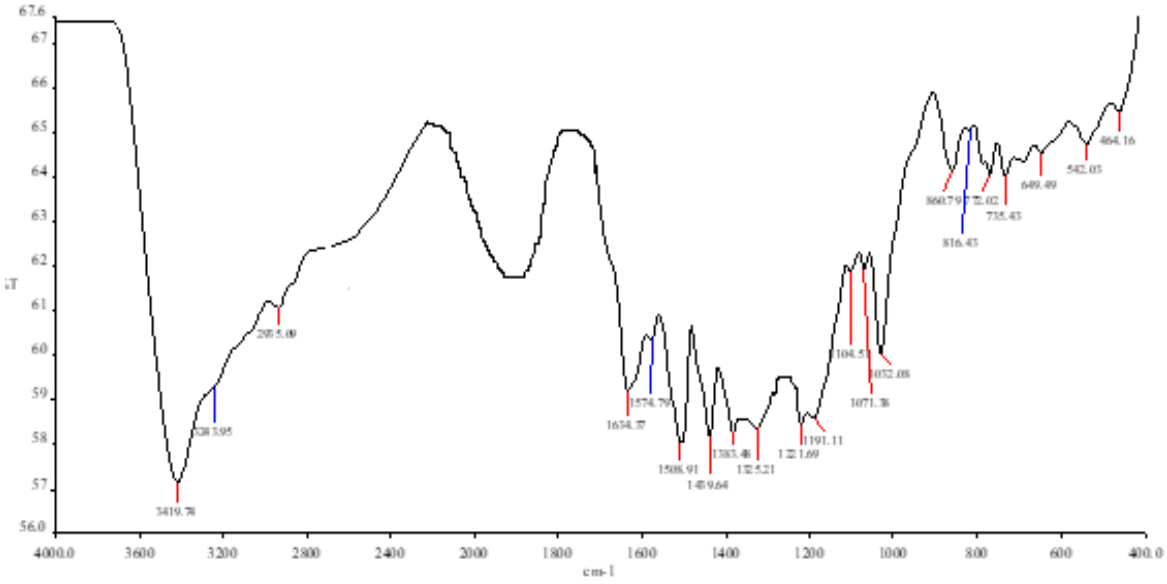
MS (m/z): Actual molecular weight (551.01 g/mol), and we found (572.32 g/mol).

4.1.5. Spectral characteristics of 3-(4-(3-chloro-4-fluorophenylamino)-6-(3-morpholinopropoxy) quinazolin-7-yloxy)-2-oxopropanoic acid (6e)



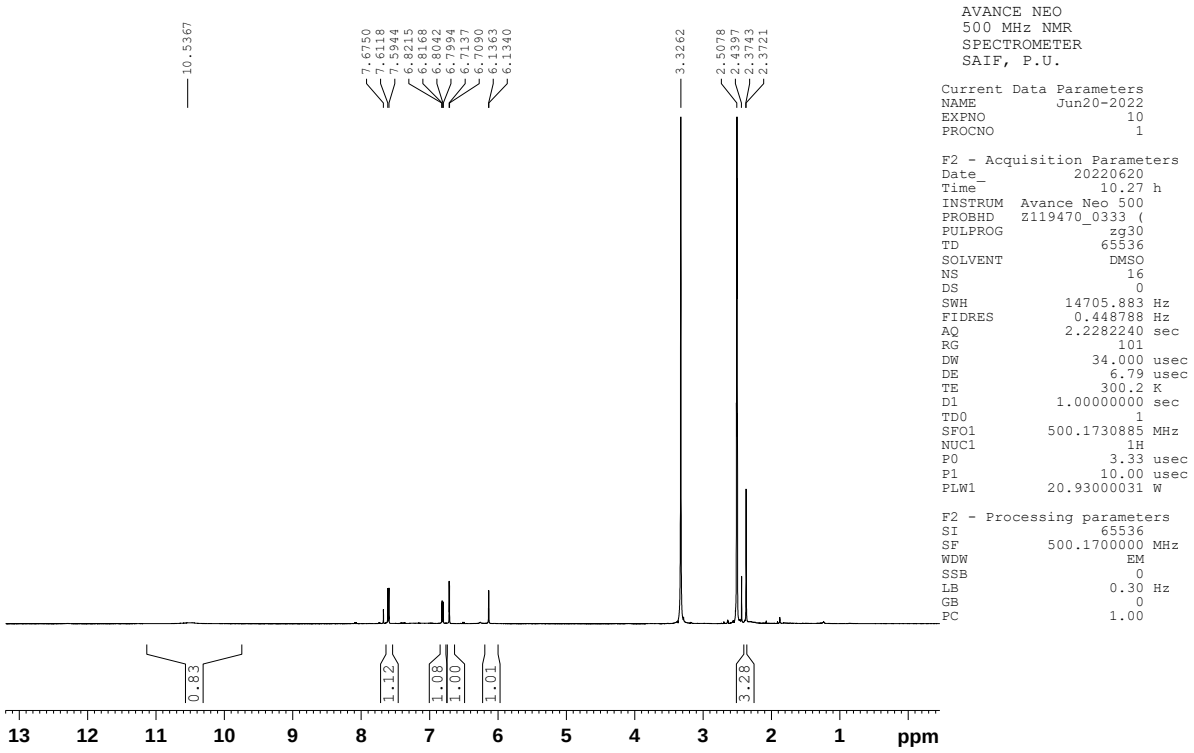
A off white Solid with Molecular formula $C_{24}H_{24}ClFN_4O_6$ and Molecular Weight 518.92g/mol yielded 55% with melting point in the range of 216 ^oC and R_f value of 0.56.

IR spectra of compound 6e



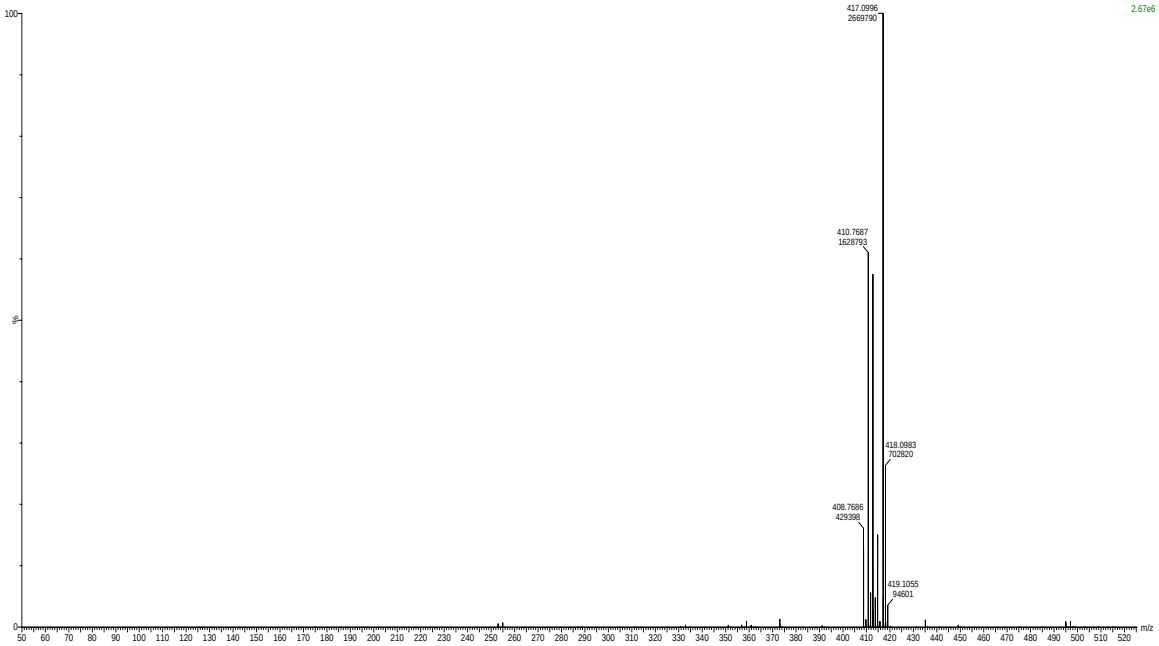
IR (cm^{-1}): The IR spectra of compounds exhibited absorption bond at 3243.95cm^{-1} (Ar-C-H stretch), 1723.55cm-1, 1650.44cm^{-1} (Ar-C=O stretch), 1590.22cm^{-1}, 1634.37cm^{-1} (Ar-C=N stretch), 1071.38cm^{-1} (Ar-C-N stretch), 1574.79cm^{-1} (Ar-C=C stretch), 1439.64cm^{-1} aromatic (=CH-sp^2 stretch), 2935.09cm^{-1} (Ar-N-H stretch), 1028cm^{-1} (CF stretch).

[1]HNMR spectra of compound 6e



[1]HNMR (DMSO-d_6, 500MHz, δ ppm): 10.53 (s, carboxylic acid C-OH), 4.0 (s, 1H, NH), 3.65-2.36 (m, Ar-H, CH_2), 4.21, 2.46, 1.82 (t, Methylene, CH_2), 5.35 (t, aromatic C-OH), 8.46, 7.41, 7.24 (t, CH, quinazoline), 6.79-7.29 (m, CH, benzene),

MS spectra of compound 6e



MS (m/z): Actual molecular weight (518.92 g/mol), and we found (5.12.32 g/mol).

4.2. EVALUATION TESTS OF THE FORMULATION OF THE TABLETS:

4.2.1. Formulations of Tablets: The tablet formulations were done by the direct compression method. And the quantity of the ingredients is given below in the table.

In formulation (1), gefitinib prodrug 6a is added. Similarly, formulation (2) Gefitinib prodrug 6b is added, formulation (3) Gefitinib prodrug 6c is added, formulation (4) Gefitinib prodrug 6d is added, and formulation (5) Gefitinib prodrug 6e is added.

In the evaluation test, formulation (F0) contains an actual Gefitinib drug, which is compared with other Gefitinib prodrug formulations of the drugs.

Table 6.2: Ratio of ingredients used in formations of tablets

S. No.	Ingredients g/ml	Formulation (1)	Formulation (2)	Formulation (3)	Formulation (4)	Formulation (5)
1.	Gefitinib Prodrug	45-55%	45-55%	45-55%	45-55%	45-55%
2.	Lactose	25-40%	25-40%	25-40%	25-40%	25-40%
3.	Micro-crystalline cellulose	5-15%	5-15%	5-15%	5-15%	5-15%
4.	Povidone	1-3%	1-3%	1-3%	1-3%	1-3%
5.	Sodium lauryl Sulphate	0.1-1%	0.1-1%	0.1-1%	0.1-1%	0.1-1%
6.	Croscarmellose Sodium	3-5%	3-5%	3-5%	3-5%	3-5%
7.	Magnesium Sterate	0.5-2%	0.5-2%	0.5-2%	0.5-2%	0.5-2%

4.2.2. General Appearance of the tablets: Which are given in below

S. No.	Physical appearance	Observation
1.	Shape	Circular
2.	Size	100 mg
3.	Color	Off white
4.	Odor	Odorless
5.	Taste	Tasteless
6.	Texture	Smooth

Table 4.3: Appearance of the tablets

1.2.3. Tablets Hardness: The hardness of all tablet formulations is given in the form of a table which is in below.

S. No.	Formulations	Hardness
1.	F0	5.8
2.	F1	6
3.	F2	7.5
4.	F3	6.5
5.	F4	8
6.	F5	8.5

Table 4.4: Hardness of the Tablets

The best weight variation in all of the tablet formulations is formulation first with value 6.

4.2.4. Weight Variation of the tablets:

S. No.	Formulations	Weight Variation
1.	F0	6.03+0.17
2.	F1	6.06 ± 0.20
3.	F2	7.43 ± 0.305
4.	F3	6.43 ± 0.208
5.	F4	8.08 ± 0.351
6.	F5	8.46 ± 0.26

Data is measured Mean ± S.D. (n=3).

Table 4.5: Weight variation of the Tablets

The best weight variation in all of the tablet formulations is formulation first.

4.2.5. Friability tests of all tablet formulations:

S. No.	Formulations	Friability
1.	F0	0.30
2.	F1	0.29
3.	F2	0.35
4.	F3	0.32
5.	F4	0.35
6.	F5	0.31

Data is measured Mean + S.D. (n=3).

Table 4.6: Friability test of the tablets

The best friability in all of the tablet formulations is formulation first with value 0.29.

4.2.6. Disintegration tests of all tablet formulations:

S. No.	Formulations	Disintegration Time (min.)
1.	F0	5:15
2.	F1	3:25
3.	F2	4:15
4.	F3	3.50
5.	F4	6:10
6.	F5	4

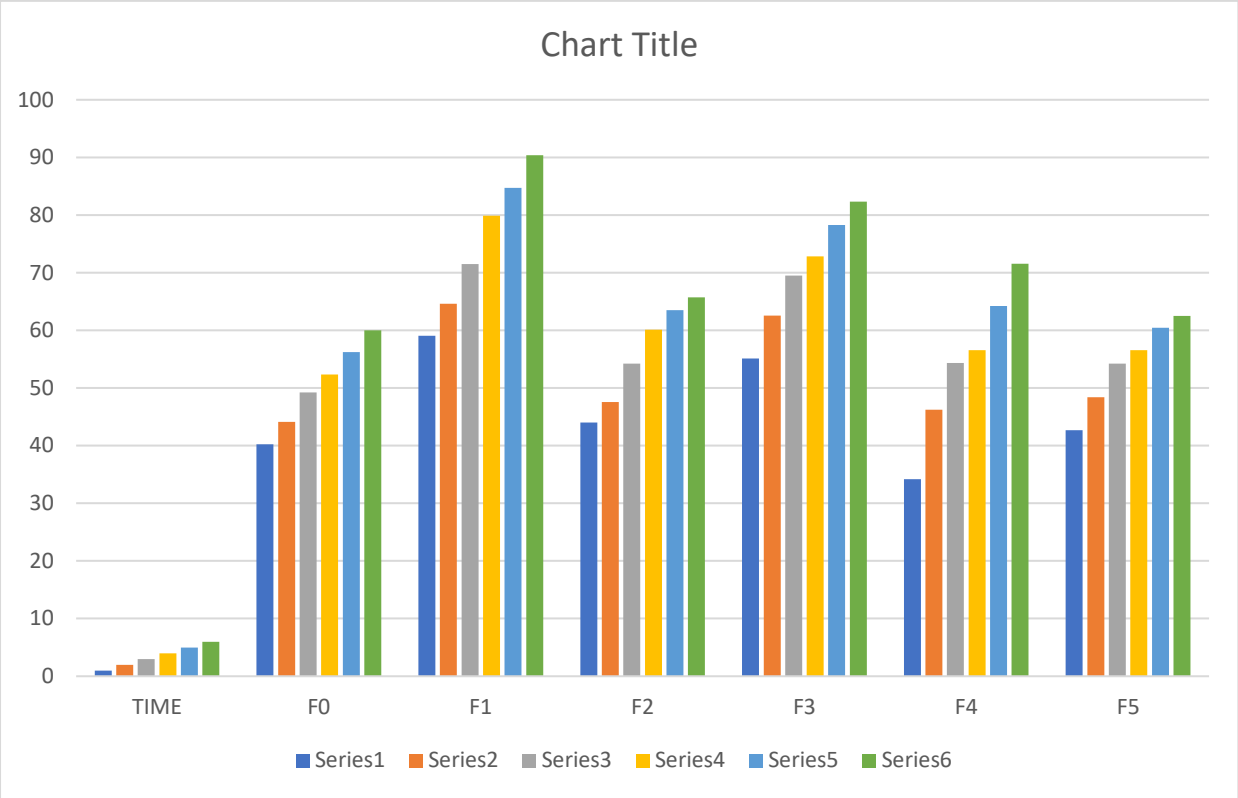
Table 4.7: Disintegration test of the tablets

The best disintegration time in all of the tablet formulations is formulation first with value 3.25.

4.2.7. Dissolution test of all tablet formulations:

Time (hr.)	F0	F1	F2	F3	F4	F5
1.	40.25%	59.04%	44.02%	55.11%	34.18%	42.66%
2.	44.11%	64.59%	47.55%	62.56%	46.24%	48.42%
3.	49.25%	71.50%	54.25%	69.50%	54.36%	54.25%
4.	52.35%	79.86%	60.14%	72.85%	56.54%	56.58%
5.	56.24%	84.72%	63.53%	78.25%	64.21%	60.44%
6.	60%	90.39%	65.72%	82.33%	71.55%	62.52%

Table 4.8: Dissolution test of the tablets



Graph: The best dissolution test in all of the tablet formulations is formulation first with release of tablet 90.39%.

5. SUMMARY AND CONCLUSION:

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer is not a single disease. It is a group of more than 200 different diseases. Cancer is the second-leading cause of death in the world. But survival rates are improving for many types of cancer, thanks to improvements in cancer screening, treatment and prevention. Most anticancer drugs have poor aqueous solubility and low permeability across the gastrointestinal tract. Gefitinib is an anticancer drug that belongs to the anilino-quinoline class. It belongs to BCS class II category having low solubility limited oral bioavailability. Treatment for lung cancer, breast cancer, and other cancers by inhibiting the activity of the protein tyrosine kinase epidermal growth factor receptor (EGFR), which has been shown to be active in non-small-cell lung cancer (NSCLC). The epidermal growth factor receptor (EGFR) protein tyrosine kinase is one of the important kinases that play a fundamental role in signal transduction pathways. Many human cancers overexpress EGFR and the related human epidermal growth factor receptor (HER-2). Compounds, such as gefitinib, that inhibit the kinase activity of EGFR. HER-2 after binding of their cognate ligand, have been used as new therapeutic antitumor agents' Potential value in the treatment of central nervous system (CNS) metastases has been rarely assessed.

But Gefitinib has major problems with solubility, dissolution, and stability of the drug. Then Present work is focused on implementation of Prodrug of anticancer drug, gefitinib (GEF) with the aim to tune its biopharmaceutical properties. Prodrugs are usually designed to enhance oral bioavailability due to poor absorption from the gastrointestinal tract. The prodrug strategy has been used to improve the selectivity of drugs. Prodrugs are used to improve how the drug is absorbed, distributed, metabolized, and excreted (ADME). After administration, it is metabolized into a pharmacologically active drug. It overcomes problems with drug delivery such as poor aqueous solubility, formulation, insufficient oral absorption, chemical instability, toxicity, and local irritation. A traditional design of anticancer prodrugs uses covalent modification by hydrophilic functionalities (e.g. phosphate, sulfate) and lipophilic moieties (e.g. Ester) to increase the aqueous solubility and passive permeability, respectively. Antioxidants (*i.e.* gallic acid, oxalic acid, ascorbic acid, Benzoic acid and Nicotinic acid) were used to create anticancer derivatives and the derivatives were combined with gefitinib to form a gefitinib prodrug. The Gefitinib prodrugs enhanced the solubility. These compounds' activities were characterised by IR spectra, mass spectra, and ^{1}HNMR spectra. Then, after spectral study, these compounds were used to formulate formulations of tablets by the compression method and perform important solubility enhancing tests like disintegration tests, dissolution tests, and friability tests. By increasing the solubility of the drug, Gefitinib prodrug shows the best results as compared to Gefitinib drug. It is also widely used in the treatment of lung and breast cancer.

The goal of this study was to synthesize, purify, characterize, and evaluate the biological activity of newly synthesised anticancer derivatives before combining them with Gefitinib drugs. In order to attain the aim, a literature survey on anticancer derivatives was carried out in the library (journals, chemical database search, and online database search (sci finder, online sites). So, I carried out an exhaustive literature survey till 2021 in order to meet the above-mentioned objectives. Then a reaction scheme for derivatives was proposed. Thionyl chloride was used in the first step to produce 3,4,5-trihydrobenzoyl chloride (1), (*R*)-5-((*R*)-2-chloro-1-hydroxyethyl)-3,4-dihydroxyfuran-2(5*H*)-one (2), nicotinoyl chloride (3), benzoyl chloride (4), and 2-chloro-2-oxoacetic acid (5). and these were clubbed with gefitinib drugs and formed a compound (6a-e). All the reaction was monitored through TLC observation till their completion using suitable each time. After the completion of the reaction, the products were dried and solvents e.g. methanol was used in final procedure.

The structures of all the synthesized derivatives were confirmed by various spectral and analytical data. The R_f value, melting point (m.p.), IR, ^{1}HNMR and mass were studied for all derivatives. The total 5 derivatives 6(a-e) were synthesized and the yield of final derivatives were found to be in the range of 55-65%. The melting point of anticancer derivative and final compounds was ranged between 220-222^{o}C and 240-260^{o}C respectively. The melting point of final compounds varied between the range of 240-246^{o}C and are uncorrected. The R_f value for all compounds were found to be in the range of 0.25-0.58 using solvent system. chloroform: Ethanol (9.5:0.5). The structure of compounds was confirmed by comparing the IR spectra, mass spectra and ^{1}HNMR spectra of final compounds.

The structure of all the synthesised derivatives was characterized on the basis of their physical and spectral data *i.e.* IR, ^{1}HNMR, MS. The IR spectra of compounds exhibited absorption bond at 3563.95cm^{-1} which confirmed the presence of aromatic C-H stretch, 1713.55 cm^{-1} which confirmed the presence of aromatic C=O stretch, 1614.37 cm^{-}which confirmed the presence of aromatic C=N stretch, 1171.38 cm^{-1} which confirmed the presence of aromatic C-N stretch, 1028 cm^{-1} which confirmed the presence of aromatic C-F stretch, 1439.64 cm^{-1} which confirmed the presence of aromatic =CH-sp^2 stretch, 1235.12 cm^{-1} which confirmed the presence of aromatic C-O stretch 2935.09 cm^{-1} which confirmed the presence of aromatic N-H stretch.

Solvent used for ^{1}HNMR spectra was DMSO. ^{1}HNMR spectra had singlet at the region of δ 3.58ppm indicated the presence of aromatic C-OH, multiplet in region δ 1.82-4.06 ppm indicated the presence of 3 aromatic protons of methylene, singlet at region of δ 5.0 ppm indicated the presence of C-H proton of furanon, singlet at region of δ 4.35 ppm indicated the presence of CH in methine, singlet at region of δ 4.00 ppm indicated the presence of aromatic C-NH proton in the compound, 4 singlet at region of δ 2.36 -3.79 ppm indicated the presence of 4 proton of CH_2 , singlet at region of δ 6.74, 7.16, 6.84, 7.29 ppm indicated the presence of 4 aromatic proton in benzene .

The mass spectra of compounds exhibited mass (m/z) in which the actual molecular weight (590.89 g/mol) and we found (572.32 g/mol) of the best compound 6a.

After the formulation of the tablets Check the solubility and stability. The best integration test all over the formulation was 3.25 min., hardness was 6, 90% of the drug was dissolute and the friability test was 0.29. According to this, the 1st formulation was the best formulation of the gefitinib prodrug, which enhanced the solubility as compared to other, mainly gefitinib drugs.

REFERENCES:

1. Dahan, A., Khamis, M., Agbaria, R. and Karaman, R., 2012. Targeted prodrugs in oral drug delivery: the modern molecular biopharmaceutical approach. *Expert opinion on drug delivery*, *9*(8), pp.1001-1013.
2. Peesa, J.P., Yalavarthi, P.R., Rasheed, A. and Mandava, V.B.R., 2016. A perspective review on role of novel NSAID prodrugs in the management of acute inflammation. *Journal of Acute Disease*, *5*(5), pp.364-381.
3. Kratz, F., Abu Ajaj, K. and Warnecke, A., 2007. Anticancer carrier-linked prodrugs in clinical trials. *Expert opinion on investigational drugs*, *16*(7), pp.1037-1058.
4. Denny, W.A., 2004. Tumor-activated prodrugs—a new approach to cancer therapy. *Cancer investigation*, *22*(4), pp.604-619.
5. Iqbal, M.S. And Sher, M., 2011. Muhammad Ajaz Hussain1, Zahid Hassan2, Muhammad Tahir Haseeb2, Mohammad Saeed Iqbal3, Muhammad Sher1, Muhammad Nawaz Tahir4, Wolfgung Tremel4, Sajid Bashir2 and Riaz Ahmad5. *Pak. J. Pharm. Sci*, *24*(4), pp.575-581.
6. Dahan, A., Khamis, M., Agbaria, R. and Karaman, R., 2012. Targeted prodrugs in oral drug delivery: the modern molecular biopharmaceutical approach. *Expert opinion on drug delivery*, *9*(8), pp.1001-1013.
7. Karaman, R., Fattash, B. and Qtait, A., 2013. The future of prodrugs–design by quantum mechanics methods. *Expert opinion on drug delivery*, *10*(5), pp.713-729.
8. Rautio, J., Kumpulainen, H., Heimbach, T., Oliyai, R., Oh, D., Järvinen, T. and Savolainen, J., 2008. Prodrugs: design and clinical applications. *Nature reviews Drug discovery*, *7*(3), pp.255-270.
9. Hamid, M.H. and Elsaman, T., 2017. A stability-indicating RP-HPLC-UV method for determination and chemical hydrolysis study of a novel naproxen prodrug. *Journal of Chemistry*, *2017*.
10. Fang, J.Y. and Al-Suwayeh, S.A., 2012. Nanoparticles as delivery carriers for anticancer prodrugs. *Expert opinion on drug delivery*, *9*(6), pp.657-669.
11. Walther, R., Rautio, J. and Zelikin, A.N., 2017. Prodrugs in medicinal chemistry and enzyme prodrug therapies. *Advanced drug delivery reviews*, *118*, pp.65-77.
12. Keefe Guang Zhi Lee[a], Maria V. Babak[a], Andrea Weiss[b], Paul J. Dyson[c], Patrycja NowakSliwinska[b]*, Diego, (2018) “Development of an Efficient Dual-action GST-inhibiting Anticancer Platinum (IV) Prodrug” p.p. 5213-5245.

13. Jain, A.K. and Jain, S., 2016. Advances in oral delivery of anti-cancer prodrugs. *Expert opinion on drug delivery*, *13*(12), pp.1759-1775.
14. Stella, V., Borchardt, R., Hageman, M., Oliyai, R., Maag, H. and Tilley, J. eds., 2007. *Prodrugs: challenges and rewards*. Springer Science & Business Media.
15. Huttunen, K.M., Raunio, H. and Rautio, J., 2011. Prodrugs—from serendipity to rational design. *Pharmacological reviews*, *63*(3), pp.750-771.
16. Huttunen, K.M., Raunio, H. and Rautio, J., 2011. Prodrugs—from serendipity to rational design. *Pharmacological reviews*, *63*(3), pp.750-771.
17. Rautio, J., Kumpulainen, H., Heimbach, T., Oliyai, R., Oh, D., Järvinen, T. and Savolainen, J., 2008. Prodrugs: design and clinical applications. *Nature reviews Drug discovery*, *7*(3), pp.255-270.
18. Fattash, B. and Karaman, R., 2014. Chemical approaches used in prodrugs design. *Nova Science Publishers, Inc. NY, USA*, pp.103-138.
19. Karaman, R., 2014. Using predrugs to optimize drug candidates. *Expert opinion on drug discovery*, *9*(12), pp.1405-1419.
20. Karaman, R., 2014. *Prodrugs Design-A New Era*. Nova Science Publishers, Incorporated.
21. Dahan, A., Zimmermann, E.M. and Ben-Shabat, S., 2014. Modern prodrug design for targeted oral drug delivery. *Molecules*, *19*(10), pp.16489-16505.
22. Grunwald, P., 2020. Enzymes for Prodrug-Activation in Cancer Therapy. In *Pharmaceutical Biocatalysis* (pp. 155-197). Jenny Stanford Publishing.
23. Yuan, Z., Yi, X., Zhang, J., Cheng, S., Zhuo, R. and Li, F., 2013. A prodrug nanoassembly entrapping drugs as a tumor-targeted delivery system. *Chemical Communications*, *49*(8), pp.801-803.
24. Zhong, Y.J., Shao, L.H. and Li, Y.A.N., 2013. Cathepsin B-cleavable doxorubicin prodrugs for targeted cancer therapy. *International Journal of Oncology*, *42*(2), pp.373-383.
25. Zhong, Y.J., Shao, L.H. and Li, Y.A.N., 2013. Cathepsin B-cleavable doxorubicin prodrugs for targeted cancer therapy. *International Journal of Oncology*, *42*(2), pp.373-383.
26. Podgorski, I. and Sloane, B.F., 2003, January. Cathepsin B and its role (s) in cancer progression. In *Biochemical Society Symposia* (Vol. 70, pp. 263-276). London; Portland on behalf of The Biochemical Society; 1999.
27. Carl, P.L., Chakravarty, P.K. and Katzenellenbogen, J.A., 1981. A novel connector linkage applicable in prodrug design. *Journal of Medicinal Chemistry*, *24*(5), pp.479-480.

28. Duncan, R., 2006. Polymer conjugates as anticancer nanomedicines. *Nature reviews cancer*, *6*(9), pp.688-701.
29. Zhang, J. and Ma, P.X., 2013. Cyclodextrin-based supramolecular systems for drug delivery: recent progress and future perspective. *Advanced drug delivery reviews*, *65*(9), pp.1215-1233.
30. Zhang, J. and Ma, P.X., 2013. Cyclodextrin-based supramolecular systems for drug delivery: recent progress and future perspective. *Advanced drug delivery reviews*, *65*(9), pp.1215-1233.