SYNTHESIS, CHARACTERIZATION AND EVALUATION OF CYTOTOXIC ACTIVITY OF NOVEL MODIFIED HETEROCYCLIC COMPOUNDS

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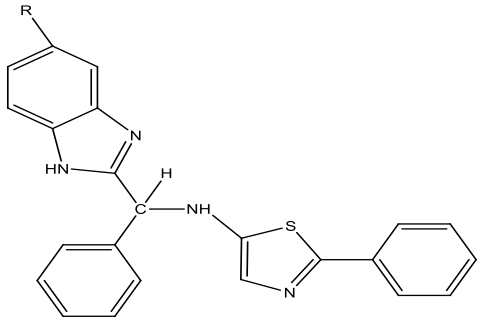
Abstract

Malignant neoplasm, another name for cancer, is a horrible condition that can invade or spread to other sections of the body due to aberrant cell proliferation. According to the World Health Organization's 2015 study, cancer causes 8.8 million deaths globally, or one in every six fatalities, with 70 percent of those deaths occurring in low- and middle-income nations. Despite the fact that there are several anticancer drugs available nowadays, certain big cancer forms are incredibly resistant to them. Due to their considerable pharmacological activity, as was already noted, benzimidazole and thiazoles are important pharmacophore in medicinal chemistry. We selected these two for our analysis because of their capacity to combat cancer. In order to construct a possible anticancer agent, certain benzimidazole derivatives were made. Here is a representation of the synthesised derivaties' model skeleton.



R= H, NO_2

Keywords: Anticancer, Benzimidazole, Cytotoxic, Cancer, Toxicity, Thiazole.

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Introduction

History of cancer:

The history of cancer is a tale of hypotheses on the causes and effects of the illness as well as ongoing detailed discoveries into its physiology, therapies, and diagnostic techniques. Moreover, this history is linked to broader advancements in medicine, including novel surgical procedures and discoveries regarding new methods and tools. In this broad sense, the history of cancer may be broken down into several eras, the first of which includes the very lengthy ancient and mediaeval eras, which were founded on what we now recognise as false assumptions about the nature of cancer. (Grooning et al., 2015).

The word "cancer" was first used by Greek physician Hippocrates (460-370 BC). The "Father of Medicine" is what they call him. Hippocrates used the words carcinoma and carcinos to refer to ulcer-producing and non-ulcer forming cancers, respectively. In Greek, this is a crab. The description was given the term "crab" because the finger-like spreading projections of cancer resembled a crab. Hippocrates is also credited with creating the term "cancer," using the name "carcinos" to refer to what seemed to be malignant growths. 2011 (Carlos P et al). The 1,300-year-old cancer theory put out by Hippocrates is based on four different body fluids. Among these are phlegm, blood, yellow bile, and black bile. A person is regarded to be healthy when their sense of humour is balanced. On the other hand, too much black bile humour led to cancer. A subsequent Roman physician named Celsus (28–50 BC) translated the Greek phrase into cancer, the Latin word for crab. Galen, a second Roman doctor who practised from 130 to 200 AD, used the Greek word oncos, which means swelling, to describe tumours. Oncos is the root word for oncology, which is the study of malignancies.

The oldest known descriptions of cancer may be found in many papyri from Ancient Egypt. A description of cancer and a method to remove breast tumours by cauterization are both found in the Edwin Smith Papyrus, which was written circa 1600 BC (perhaps a part of a 2500 BC work). The papyrus humorously remarks that the illness has no cure. (2011) Carlos P. et al.

Basics about cancer

Cancer is characterised by unchecked cell proliferation in the body. These aberrant cells in the body are referred to as cancer cells, malignant cells, or tumour cells. These cells are able to invade healthy bodily tissues. The designation of the tissue from which the aberrant cells originated helps to further differentiate many malignancies and the abnormal cells that make up cancer tissue (for example, breast cancer, lung cancer and colorectal cancer). A mass of cancer cells develops when damaged or unrepaired cells in the body do not perish but instead transform into cancer cells with unchecked cell proliferation and cell expansion. Cancerous cells have the ability to separate from their initial cell mass, migrate via the blood and lymphatic systems, and settle in other organs, where they can continue their unchecked cycle of development. Metastatic spread, also known as metastasis, is the process through which cancer cells move to new locations. For instance, a person gets bone metastatic breast cancer if breast cancer cells have spread to a bone (Kamari et.al. 2017).

Difference between normal cell and cancer cell

Cancer cells disobey the body's warnings to cease dividing. Your body has a natural mechanism called apoptosis, sometimes known as "programmed cell death," that instructs it to get rid of cells that are no longer needed. Normal cells are more receptive to stimuli from the body and cease replicating when there are sufficient numbers of cells.

Several cell types are formed as normal cells differentiate. These distinct cell types have different functions. For instance, liver cells help your body break down proteins, lipids, and carbs while also clearing your blood of alcohol. Since cancerous cells divide so fast, they are never given the chance to develop into the specialised cells for which they were intended.

In the proximity of a tumour, cancer cells may affect the behaviour of healthy blood vessels, chemicals, and cells. For instance, cancer cells may entice healthy cells to develop new blood vessels. These veins provide the tumour the oxygen and nourishment it needs to stay alive and develop. The immune system often gets rid of aberrant or damaged cells. This

procedure can be avoided by cancer cells, allowing tumours to spread.

Cancer cells invade adjacent tissues because they disobey the body's instructions to cease proliferating. A benign tumour won't infiltrate nearby tissues; it will only bump up against them. On the other hand, a malignant tumour invades tissue and has the ability to grow throughout the body. Normal cells locate their proper locations in your body and remain there. Metastatic cancer cells are those that have spread to other areas of the body. For instance, cancer might start in the lungs and progress to the liver. Instead of liver cancer, it is referred to as metastatic lung cancer if this spread takes place.

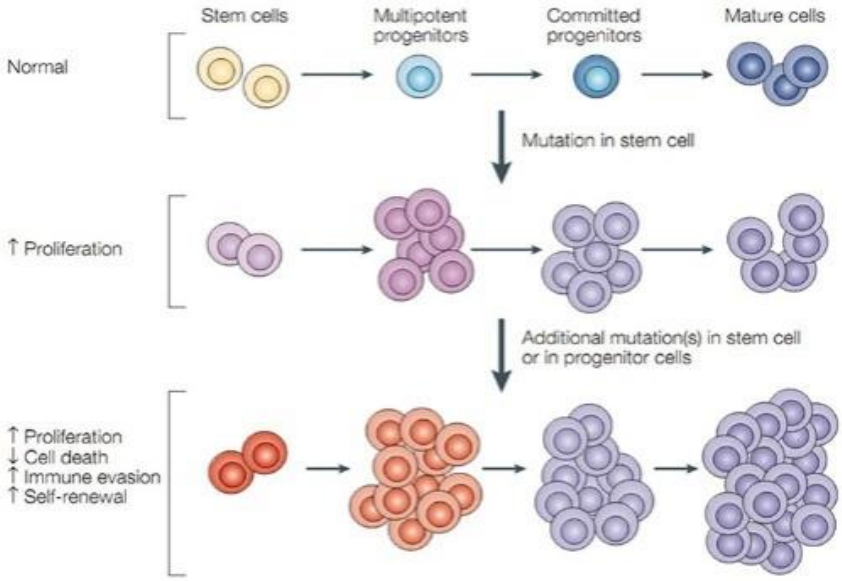


Figure. No 2: Difference between normal cell and cancerous cell (Frontier Journal)

Benzimidazole: Benzimidazole is a fragrant heterocyclic chemical molecule. This bicyclic molecule is formed through the fusion of benzene and imidazole. This vital group of chemicals has had practical uses in a variety of industries. Benzimidazole has isosteric relationships with indole and purine nuclei, which are found in a variety of essential cell components and bioactive chemicals. This Heterocycles may potentially represent a type of privileged substructure, which may interact with specific proteins and enzymes. The importance of purines in the organic gadget became established in the early 1950s, and it turned into discovered that five, 6-dimethyl-1-(D-ribofuranosyl) benzimidazole is an important element of the structure of Vit.B12 (Tonelli et al 2010, Wright et al).

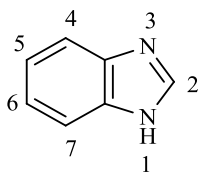
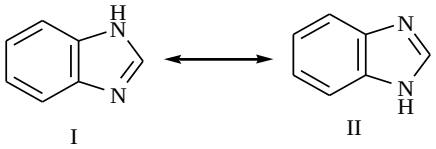


Fig. No 3: Benzimidazole

Benzimidazole which incorporate a hydrogen atom connected to nitrogen in the1-position comfortably tautomerize. This tautomerism is analogous to that observed within the imidazoles and amidines. This can be depicted as follows:



I II

Fig.No 4: Tautomerism of Benzimidazole

Benzimidazole is represented as (I), with a proton at N1 and a quick exchange of –NH and =N- nitrogen atoms. Tautomerism (I) and (II) are caused by an intermolecular reaction involving two or more benzimidazole molecules or by interaction with aprotic solvent such as water. The groups in the ring system at positions C5 and C6 are chemically identical (Preston, 1981).

Reaction mechanism of synthesis of benzimidazole:

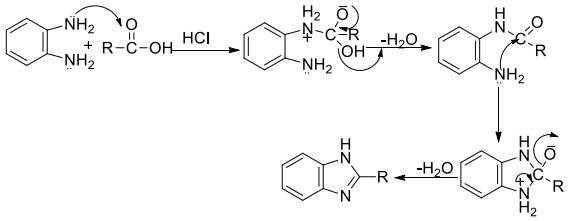


Fig. No 5: Mechanism of action of Benzimidazole

A total of 15,000 medications are now being used in clinical settings, while 10,000 drug-like substances are through different phases of clinical development. Many heterocyclic nuclei, including indole, benzimidazole, quinoline, phenothiazine, tricyclic rings (dibenzothiazine, dibenzoxazine), and piperazine are significant pharmacophores, according to a thorough analysis of these compounds.

Benzimidazole is one of the most often utilised nuclei. In the list of chemotherapeutic medications, it holds a prominent position thanks to its vast pharmacological action.

Early in the 1950s was a crucial time for understanding the biological significance of benzimidazole and the closely related purines; the critical function of purines in the biological system was established, and it was found that vitamin B12's structure includes 5, 6-dimethyl-1-(-D-ribofuranosyl) benzimidazole.

The chemistry of imidazoles and related compounds has attracted a great deal of attention as a result of these discoveries, and significant progress has been made in this area. As a result, a new class of benzimidazole derivatives with antibacterial, antifungal, anthelmintic, anticancer, and proton pump inhibitor properties has been produced. The benzimidazole nucleus has also been utilised in a number of therapeutic categories, including the antiemetic Domperidone (Janssen 1978), anthelmintic Albendazole (GSK, 1982), coronary vasodilator Bendazol (GSK, 1982), omeprazole (Astra Zeneca, 1988), lansoprazole (Takeda, 1992), and pantoprazole.

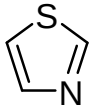
Table No 1: Physical Properties of Benzimidazole

Molecular Formula	$C_7H_6N_2$
Molecular Weight	118.149 g/mol
Log P Value	1.67
PKa	2.5 (Strong Basic)
Melting Point	170.5

Thiazole

The word "thiazole," also known as "1, 3-thiazole," refers to a large family of derivatives that are all heterocyclic molecules that include both sulphur and nitrogen. Thiazole is a chemical compound having the colourless, odourless liquid formula C3H3NS. Because the thiazole ring is a part of the vitamin thiamine, it is significant (B1).

The azole family, which also comprises imidazoles and oxyazoles, includes heterocycles such as thiazoles. Another way to think of thiazole is as a functional group. Similar compounds called oxyazoles have sulphur substituted with oxygen. Similar to imidazoles in structure, thiazoles have the thiazole sulphur replaced by nitrogen. Thiazole rings are planar and aromatic. Thiazoles exhibit more pi-electron delocalization than similar Oxazoles, which increases their aromaticity. Proton NMR spectroscopy's chemical shift of the ring protons (between 7.27 and 8.77 ppm) points to a sizable diamagnetic ring current. According to the calculated pi-electron density, C5 is the main site for electrophilic substitution while C2 is the main site for nucleophilic substitution. (Wikipedia)



1,3-thiazole

Fig No 6: Structure of Thiazole

Table No 2: Physical Properties of Thiazole

Chemical Names	1, 3-Thiazole
Molecular Formula	C_3H_3NS
Molecular Weight	85.12 g·mol^{-1}
Log P Value	**0.89**
PKa	2.5 (of conjugate acid)
Melting Point	**117-118 °C**
Boiling Point	116 to 118 °C (241 to 244 °F; 389 to 391 K)
Solubility	Thiazole is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF).

Materials and Methods:

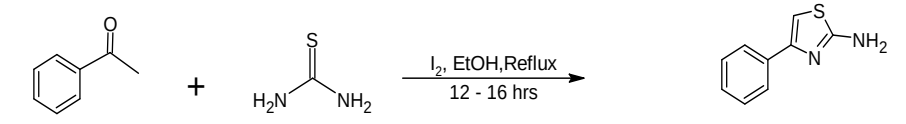
All of the chemicals were from Thomas's Baker, Sigma Aldrich, and SD Fine Chemicals. The reagent grade solvents that were utilised were all purchased from Sigma Aldrich, SD Fine Chemicals, and Thomas' Baker. Using 50 F254 precoated silica gel plates from Merck, thin-layer chromatography (TLC) was used to identify the reactants and products that were being monitored both throughout the course of the reaction and after it had finished. The dots were seen in an enclosed chamber with iodine fumes or in a UV chamber. The uncorrected melting points were all calculated using Thiel's tube melting points device. IR spectra were recorded on KBr pellets on a shimadzu 1000 FTIR spectrometer in the range of 4000-200 cm^{-1}, Resolution 2.0 with No. of scan- 45. Apodization; Happ-Genzel. Proton resonance magnetic spectra (^{1}H NMR) were recorded on Bruker 400MHz spectrophotometer using d_5-DMSO as solvent and chemical shifts were expressed in parts per million (δ ppm), downfield from TMS as an internal standard. Mass spectra (MS) were recorded on LCMS instrument with APCI as well as on 4000Q – TRAP MS/MS System. To examine cytotoxic effects, bendamustin injection IP, commercialised under the trade name Xyotin and containing bendamustin 100 mg/mL, was utilised as the control medication. Miracalus Pharmaceuticals Pvt. Ltd.

Experimental Section:

Synthesis of 4-(phenyl)-1, 3-thiazol

To obtain aminothiazole-phenone, acetophenone (1.0 equiv) was reacted with iodine (1.1 equiv) and thiourea (3.0 equiv) in ethanol under reflux condition for 12.0–15.0 h. Then, the reaction mixture was quenched with NaOH (aq) (2.0 equiv) and the ethanol was removed under reduced pressure.

The residue was extracted with ethyl acetate and the combined organic layer were washed the brine and dried over MgSO4(s). After being filtered and condensed under reduced pressure, the crude product was purified by column chromatography on silica gel (ethyl acetate and hexane as eluent) to give compound (Huang et al. (2015)).



1-phenylethan-1-one thiourea 4-phenyl-1,3-thiazol-2-amine

Figure No 7: Synthesis of 4-(phenyl)-1, 3-thiazol

Synthesis of Product: Step 1

Synthesis of (1H-benzo[d] imidazol-2-yl) (phenyl) methanol

Orthophenylene diamine (5 gm, 0.045 mol) and mandellic acid (5 gm, 0.032 mol) in 4N HCl (9 mL) was taken in RBF. Reaction mixture was heated on heating mantle and keep in refluxing condition for about 02 hours at 80^{0}C. The progress of the reaction is monitored by thin layer chromatography (TLC). Upon completion of the reaction, solid precipitate is obtained after the neutralization of reaction mixture by using 10 $NaHCO_3$. The crude product recrystallized by using Ethanol.

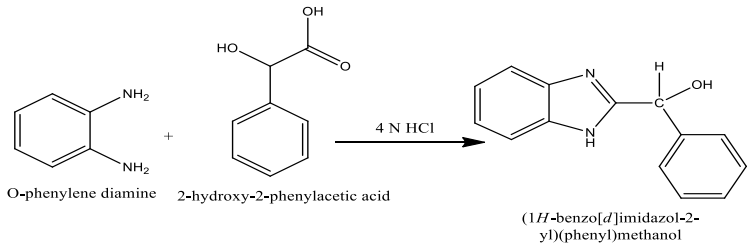


Figure No 8: Synthesis of (1H-benzo[d] imidazol-2-yl) (phenyl) methanol

Synthesisof (5-nitro-1H-benzo[d]imidazol-2-yl) (phenyl) methanol

4-Nitro Orthophenylene diamine (3 gm, 0.019 mol) and mandellic acid (3 gm, 0.019 mol) in 4N HCl (9 mL) was taken in RBF. Reaction mixture was heated on heating mantle and keep in refluxing condition for about 02 hours at 80^0C. The progress of the reaction is monitored by thin layer chromatography (TLC). Upon completion of the reaction, solid precipitate is obtained after the neutralization of reaction mixture by using 10 $NaHCO_3$. The crude product recrystallized by using Ethanol.

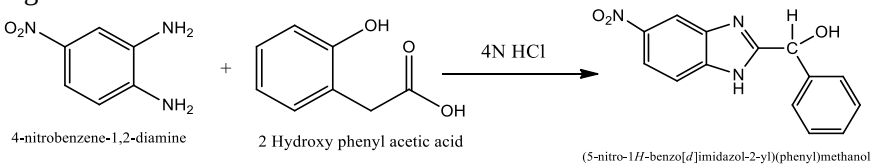


Figure No 9: Synthesis of (5-nitro-1H-benzo[d]imidazol-2-yl) (phenyl) methanol

Synthesis of 3-(1H-benzo[d]imidazol-2-yl) propionic acid

Orthophenylene diamine (4 gm, 0.037 mol) and 3-chloropropionic acid (5 gm, 0.055 mol) were weighed separately and transferred to a round bottom flask. To the above mixture, 200 ml of 5 N HCl was added and refluxed for 8 hours. Reaction completion was monitored by TLC.Solution was allowed to stand overnight, filtered and the filtrate was cooled by the addition of ice. It was then neutralized by careful addition of solid $NaHCO_3$ by stirring. Product was removed by filtration, washed with water and dried. Recrystallization was done using ethanol.

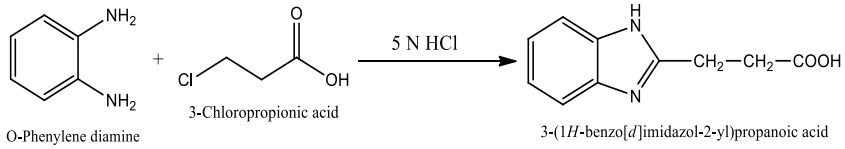


Figure No 10: Synthesis of 3-(1H-benzo[d]imidazol-2-yl) propionic acid

Synthesis of 3-(5-nitro-1H-benzo[d]imidazol-2-yl) propionic acid

4-Nitro Orthophenylene diamine (2 gm, 0.013 mol) and 3-chloropropionic acid (4 gm, 0.035 mol) were weighed separately and transferred to a round bottom flask. To the above mixture, 200 ml of 5 N HCl was added and refluxed for 8 hours. Reaction completion was monitored by TLC.Solution was allowed to stand overnight, filtered and the filtrate was cooled by the addition of ice. It was then neutralized by careful addition of solid $NaHCO_3$ by stirring. Product was removed by filtration, washed with water and dried. Recrystallization was done using ethanol.

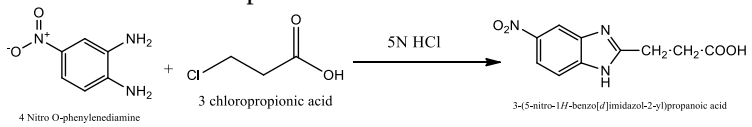


Figure No11: Synthesis of 3-(5-nitro-1H-benzo[d]imidazol-2-yl) propionic acid

Synthesis of 4-(1H-benzo[d]imidazole-2-yl) butanoic acid

Orthophenylene diamine (2 gm, 0.0185 mol) and 4-chlorobutyric acid (4 gm, 0.032mol) were weighed separately and transferred to a round bottom flask. To the above mixture, 15 ml of 4N HCl was added and refluxed for 5 hours. Reaction completion was monitored by

TLC. Reaction mixture was cooled and neutralized by careful addition of Ammonia by stirring. Product was removed by filtration, washed with water and dried. Recrystallization was done using ethanol.

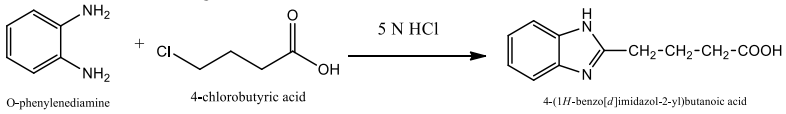


Figure No 12: Synthesis of 4-(1H-benzo[d]imidazole-2-yl) butanoic acid

Synthesis of 4-(5-nito-1H-benzo[d]imidazol-2-yl) butanoic acid

4-Nitro Orthophenylene diamine (3 gm, 0.0195 mol) and 4-chlorobutyric acid (5 gm, 0.0489 mol) were weighed separately and transferred to a round bottom flask. To the above mixture, 15 ml of 4N HCl was added and refluxed for 5 hours. Reaction completion was monitored by TLC. Reaction mixture was cooled and neutralized by careful addition of Ammonia by stirring. Product was removed by filtration, washed with water and dried. Recrystallization was done using ethanol.

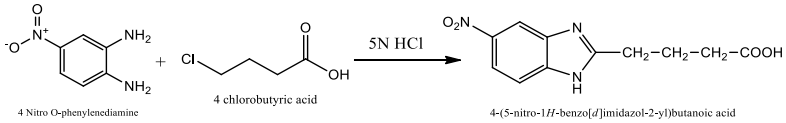


Figure No 13: Synthesis of 4-(5-nito-1H-benzo[d]imidazol-2-yl) butanoic acid

Synthesis of Intermediates: Step 2

Synthesis of 2-(chloro (phenyl) methyl)-1H-benzo[d]imidazole

In a 250 ml three neck RBF, 24 ml (0.201mol) thionyl chloride was transferred and the RBF was placed in an ice cold water bath. To it 4 gm (0.017mol) of (1H-benzo[d] imidazol-2-yl) (phenyl) methanol (step 1 product) was added slowly with occasionally shaking. Then placed RBF on heating mantel, fitted with a condenser and refluxed for 4 hrs. Excess thionyl chloride was recovered under vacuum on water bath. To the residue dry dioxane was added and stirred for half hour. Dioxane was recovered under vacuum to get product. The progress of the reaction is monitored by thin layer chromatography (TLC). The crude product recrystallized by using Ethanol.

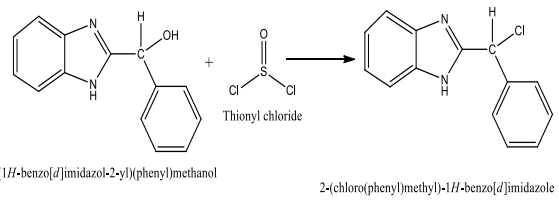


Figure No14: Synthesis of 2-(chloro (phenyl) methyl)-1H-benzo[d]imidazole

Synthesis of 2-(chloro (phenyl) methyl)-5-nitro-1H-benzo[d]imidazole

In a 250 ml three neck RBF, 24 ml (0.201 mol) thionyl chloride was transferred and the RBF was placed in an ice cold water bath. To it 4 gm (0.014 mol) of (5-nitro-1H-benzo[d]imidazol-2-yl) (phenyl) methanol (step 1 product) was added slowly with occasionally shaking. Then placed RBF on heating mantel, fitted with a condenser and refluxed for 4 hrs. Excess thionyl chloride was recovered under vacuum on water bath. To the residue dry dioxane was added and stirred for half hour. Dioxane was recovered under vacuum to get product. The progress of the reaction is monitored by thin layer chromatography (TLC). The crude product recrystallized by using Ethanol.

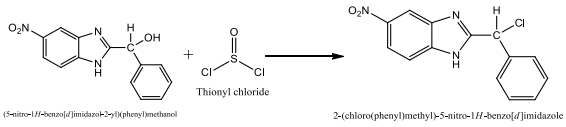


Figure No 15: Synthesis of2-(chloro (phenyl) methyl)-5-nitro-1H-benzo[d]imidazole

Synthesis of 3-(1H-benzo[d]imidazol-2-yl) propanoyl chloride

In a 250 ml three neck RBF, 30 ml (0.25 mol) thionyl chloride was transferred and the RBF was placed in an ice cold water bath. To it 5 gm (0.025mol) of 3-(1H-benzo[d]imidazol-2-yl) propanoic acid (step 1 product) was added slowly with occasionally shaking. Then placed RBF on heating mantel, fitted with a condenser and refluxed for 4 hrs. Excess thionyl chloride was recovered under vacuum on water bath. To the residue dry dioxane was

added and stirred for half hour. Dioxane was recovered under vacuum to get product. The progress of the reaction is monitored by thin layer chromatography (TLC). The crude product recrystallized by using Ethanol.

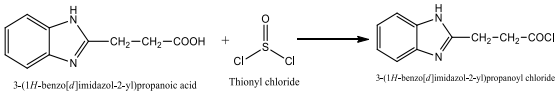


Figure No 16: Synthesis of 3-(1H-benzo[d]imidazol-2-yl) propanoyl chloride

Synthesis of3-(5-nitro-1H-benzo[d]imidazol-2-yl) propanoyl chloride

In a 250 ml three neck RBF, 5 ml (0.050mol) thionyl chloride was transferred and the RBF was placed in an ice cold water bath. To it 1 gm (0.004 mol) of 3-(5-nitro-1H-benzo[d]imidazol-2-yl) propanoic acid (step 1 product) was added slowly with occasionally shaking. Then placed RBF on heating mantel, fitted with a condenser and refluxed for 4 hrs. Excess thionyl chloride was recovered under vacuum on water bath. To the residue dry dioxane was added and stirred for half hour. Dioxane was recovered under vacuum to get product. The progress of the reaction is monitored by thin layer chromatography (TLC). The crude product recrystallized by using Ethanol.

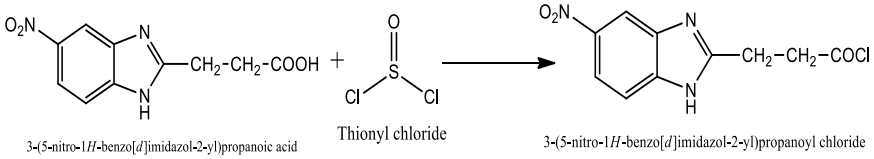


Figure No 17: Synthesis of3-(5-nitro-1H-benzo[d]imidazol-2-yl) propanoyl chloride

Synthesis of4-(1H-benzo[d]imidazol-2-yl) butanoyl chloride

In a 250 ml three neck RBF, 5 ml (0.050 mol) thionyl chloride was transferred and the RBF was placed in an ice cold water bath. To it 1 gm (0.004 mol) of 4-(1H-benzo[d]imidazole-2-yl) butanoic acid (step 1 product) was added slowly with occasionally shaking. Then placed RBF on heating mantel, fitted with a condenser and refluxed for 4 hrs. Excess thionyl chloride was recovered under vacuum on water bath. To the residue dry dioxane was added and stirred for half hour. Dioxane was recovered under vacuum to get product. The progress of the reaction is monitored by thin layer chromatography (TLC). The crude product recrystallized by using Ethanol.

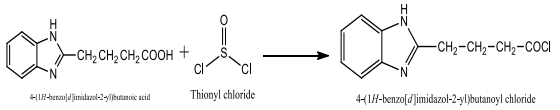


Figure No 18: Synthesis of4-(1H-benzo[d]imidazol-2-yl) butanoyl chloride

Synthesis of 4-(5-nitro-1H-benzo[d]imidazol-2-yl) butanoyl chloride

In a 250 ml three neck RBF, 5 ml (0.0050mol) thionyl chloride was transferred and the RBF was placed in an ice cold water bath. To it 1 gm (0.0040 mol) of 4-(5-nito-1H-benzo[d]imidazol-2-yl) butanoic acid (step 1 product) was added slowly with occasionally shaking. Then placed RBF on heating mantel, fitted with a condenser and refluxed for 4 hrs. Excess thionyl chloride was recovered under vacuum on water bath. To the residue dry dioxane was added and stirred for half hour. Dioxane was recovered under vacuum to get product. The progress of the reaction is monitored by thin layer chromatography (TLC). The crude product recrystallized by using Ethanol.

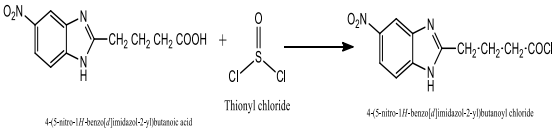


Figure No 19: Synthesis of 4-(5-nitro-1H-benzo[d]imidazol-2-yl) butanoyl chloride

Synthesis of Step-3

Synthesis of Derivatives

D1- N-((1*H*-benzo[*d*]imidazol-2-yl) (phenyl) methyl)-2-phenylthiazol-5-amine

A solution of 2-(chloro (phenyl) methyl)-1H-benzo[d]imidazole (step 2 product) (1gm, 0.0041mol) and 4-phenyl-1, 3-thiazol-2-amine (0.2 gm, 0.0011 mol) in N, N-dimethylformaide was taken in RBF. K_2CO_3 (1 gm, 0.0072 mol) was added to the reaction mixture. The reaction mixture was stirred for

2-3 h at 80°C on magnetic stirrer (heating+ stirring). The progress of the reaction was monitored by TLC. Upon completion of the reaction, water was added to the reaction mixture and the product extracted by shaking the reaction mixture with ethyl acetate in a separating funnel. The ethyl acetate layer was collected and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the product. Product Recrystallized using ethanol.

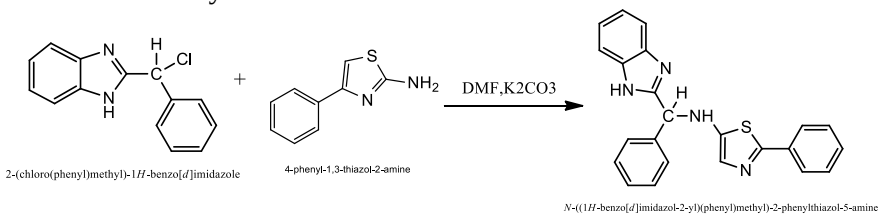


Figure No 20: Synthesis of N-((1*H*-benzo[*d*]imidazol-2-yl) (phenyl) methyl)-2-phenylthiazol-5-amine

D2-Synthesis of N-((5-nitro-1*H*-benzo[*d*]imidazol-2-yl) (phenyl) methyl)-2-phenylthiazol-5-amine

A solution of 2-(chloro (phenyl) methyl)-5-nitro-1H-benzo[d]imidazole (step 2 product) (1gm, 0.0034 mol) and 4-phenyl-1, 3-thiazol-2-amine (0.2 gm, 0.0011 mol) in N, N-dimethylformaide was taken in RBF. K_2CO_3 (1 gm, 0.0072 mol) was added to the reaction mixture. The reaction mixture was stirred for 2-3 h at 80°C on magnetic stirrer (heating+stirring). The progress of the reaction was monitored by TLC. Upon completion of the reaction, water was added to the reaction mixture and the product extracted by shaking the reaction mixture with ethyl acetate in a separating funnel. The ethyl acetate layer was collected and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the product. Product Recrystallized using ethanol.

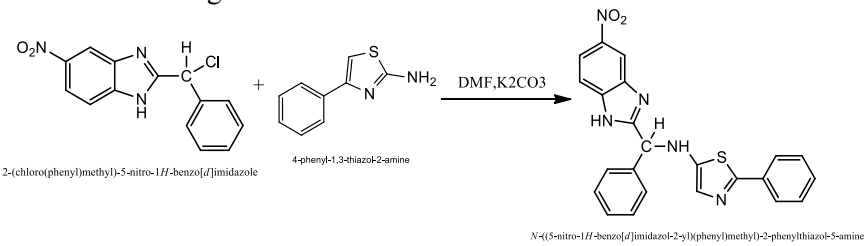


Figure No 21: Synthesis of N-((5-nitro-1*H*-benzo[*d*]imidazol-2-yl) (phenyl) methyl)-2-phenylthiazol-5-amine

D3- Synthesis of N-(2-(1*H*-benzo[*d*]imidazol-2-yl) ethyl)-2-phenylthiazol-5-amine

A solution of 3-(1H-benzo[d]imidazol-2-yl) propanoyl chloride (step 2 product) (1gm, 0.0047 mol) and 4-phenyl-1, 3-thiazol-2-amine (0.2 gm, 0.0011 mol) in N, N-dimethylformaide was taken in RBF. K_2CO_3 (1 gm, 0.0072 mol) was added to the reaction mixture. The reaction mixture was stirred for 2-3 h at 80°C on magnetic stirrer (heating+stirring). The progress of the reaction was monitored by TLC. Upon completion of the reaction, water was added to the reaction mixture and the product extracted by shaking the reaction mixture with ethyl acetate in a separating funnel. The ethyl acetate layer was collected and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the product. Product Recrystallized using ethanol.

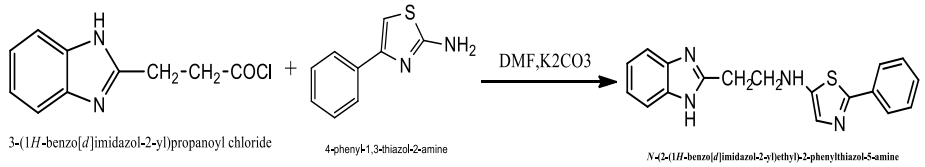


Figure No 22: Synthesis of N-(2-(1*H*-benzo[*d*]imidazol-2-yl) ethyl)-2-phenylthiazol-5-amine

D4- Synthesis of N-(2-(5-nitro-1*H*-benzo[*d*]imidazol-2-yl) ethyl)-2-phenylthiazol-5-amine

A solution of 3-(5-nitro-1H-benzo[d]imidazol-2-yl) propanoyl chloride (step 2 product) (1gm, 0.0039mol) and 4-phenyl-1, 3-thiazol-2-amine (0.2 gm, 0.0011mol) in N, N-dimethylformaide was taken in RBF. K_2CO_3 (1 gm, 0.0072 mol) was added to the reaction mixture. The reaction mixture was stirred for 2-3 h at 80°C on magnetic stirrer (heating+stirring). The progress of the reaction was monitored by TLC. Upon completion of the reaction, water was added to the reaction mixture and the product extracted by shaking the reaction mixture with ethyl acetate in a separating funnel. The ethyl acetate layer was collected and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the product. Product Recrystallized using ethanol.

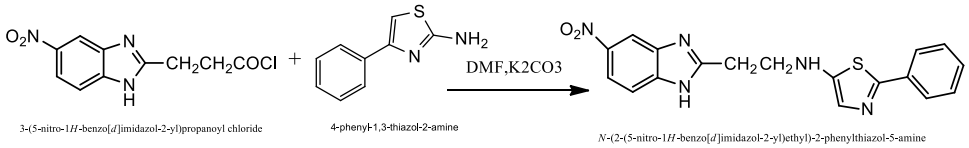


Figure No 23: Synthesis of N-(2-(5-nitro-1*H*-benzo[*d*]imidazol-2-yl) ethyl)-2-phenylthiazol-5-amine

D5- Synthesis of N-(3-(1*H*-benzo[*d*]imidazol-2-yl) propyl)-2-phenylthiazol-5-amine

A solution of 4-(1H-benzo[d]imidazol-2-yl) butanoyl chloride (step 2 product) (1gm, 0.0047 mol) and 4-phenyl-1, 3-thiazol-2-amine (0.2 gm, 0.0011 mol) in N, N-dimethylformaide was taken in RBF. K_2CO_3 (1 gm, 0.0072 mol) was added to the reaction mixture. The reaction mixture was stirred for 2-3 h at 80°C on magnetic stirrer (heating+stirring). The progress of the reaction was monitored by TLC. Upon completion of the reaction, water was added to the reaction mixture and the product extracted by shaking the reaction mixture with ethyl acetate in a separating funnel. The ethyl acetate layer was collected and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the product. Product Recrystallized using ethanol.

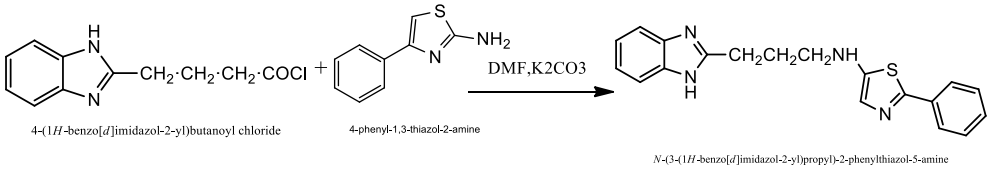


Figure No 24: Synthesis of N-(3-(1*H*-benzo[*d*]imidazol-2-yl) propyl)-2-phenylthiazol-5-amine

D6- Synthesis of N-(3-(5-nitro-1*H*-benzo[*d*]imidazol-2-yl) propyl)-2-phenylthiazol-5-amine

A solution of 4-(5-nitro-1H-benzo[d]imidazol-2-yl) butanoyl chloride (step 2 product) (1gm, 0.0037 mol) and 4-phenyl-1, 3-thiazol-2-amine (0.2 gm, 0.0011mol) in N, N-dimethylformaide was taken in RBF. K_2CO_3 (1 gm, 0.0072 mol) was added to the reaction mixture. The reaction mixture was stirred for 2-3 h at 80°C on magnetic stirrer (heating+stirring). The progress of the reaction was monitored by TLC. Upon completion of the reaction, water was added to the reaction mixture and the product extracted by shaking the reaction mixture with ethyl acetate in a separating funnel. The ethyl acetate layer was collected and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the product. Product Recrystallized using ethanol.

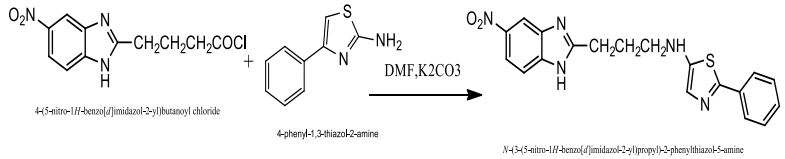


Figure No 25: Synthesis of N-(3-(5-nitro-1*H*-benzo[*d*]imidazol-2-yl) propyl)-2-phenylthiazol-5-amine

Pharmacological evaluation

Brine shrimp lethality bioassay

A bioassay measuring the mortality of brine shrimp was used to examine the cytotoxicity of the synthetic chemical. The brine shrimp lethality bioassay is simple to use, inexpensive, and only requires a little quantity of test substance. This offers an initial screening method that can be supported by more expensive and precise bioassays.

Successful usage of this *in vitro* fatality assay in the early investigation of anticancer drugs (McLaughlin et al. 1998).

Preparation of brine solution

38 g of iodize sodium chloride was weighed, dissolved in 1000 ml of distilled water and filtered to obtain a clear solution.

Hatching of *Artemia cyst* shrimps

Using brine shrimp eggs and artificial sea water, brine shrimp (*Artemia cyst*) were successfully born after 48 hours of continuous aeration. To conduct the test, the active shrimp (nauplii, larvae) were gathered.

Preparation of sample solution

10 mg each of compounds was dissolved in 10 ml of DMSO to obtain the stock concentration of 1000 µg/ml and then stock solution was diluted to various concentrations 100, 10, 1 µg/mL. In order to prevent the toxicity results from possible false effect originated from DMSO's toxicity, stock solutions of the compounds were prepared according to suggested volume range by dissolving in DMSO. Pure DMSO was used as a positive control for the toxicity assay (Nadeem et al. 2010).

Application of test solution and larvae to the test tubes

About 5 ml of brine solution was taken into each test tube. Suitable dilutions of the test substance were made as per the concentration. The 0.05 ml diluted test solution was added to the test tubes.

- 30 active shrimps (larvae) were added into each test tube
- The solution should be mixed thoroughly
- The surviving (larvae) shrimps were counted after 24 hours and lethality concentration LC50 was assessed.

Results and Discussion

Spectral analysis of Derivatives:

The final derivatives were synthesized according to the literature procedure from benzimidazole moiety and thiazole moiety. Total 6 final derivatives were synthesized. Yield, melting point and R_f values (TLC) were calculated for all 6 derivatives. The derivatives were characterized by IR and ^{1}H NMR

The IR spectra of the derivatives were measured in the region 4000-200 cm^{-1} and showed changes when compared to those of the intermediates. IR spectra of derivatives show absorptions in the 3500-650 cm^{-1}.

The insolubility of the compounds in the other organic solvents made it necessary to record ^{1}H NMR spectra in DMSO. Most of the absorption bands for the derivatives were shifted to a down field after derivatization.

Derivatives

D1- N-((1*H*-benzo[*d*]imidazol-2-yl) (phenyl) methyl)-2-phenylthiazol-5-amine

M.P-182-184°C, % Yield- 44.8%, IR (KBr) (cm-1) - 2869 (N-H) stretch, 2623 (C-H) stretch, 1600 and 1465 (C=C) stretch, 1340 Aromatic C-N vibration, 1631 (C-H) bending. NMR- 7.4-7.5 -Ar-H (Ha), 7.2-7.3 -Ar-H (Hb), 6.8 -C-H (Hc), 7.6-8.0- Ar-H (Hd), 5.0 -N-H (He), 5.4 -C-H (Hf), 4.0 -N-H (Hg).

D2- N-((5-nitro-1*H*-benzo[*d*]imidazol-2-yl) (phenyl) methyl)-2-phenylthiazol-5-amine

M.P- 164-166°C, % Yield- 60.8%, IR (KBr) (cm-1) - 2926 (C-H) stretch, 2866 (N-H) stretch, 1122 (C-N) Vibration, 1622 (C-H) bending, 1533 (N-O) stretch. NMR – 7.0-7.2- Ar-H (Ha), 5.0 – N-H (Hb), 7.2-7.3- Ar-H (Hc), 6.8- C-H (Hd), 7.4-8.0- Ar-H (He), 5.4- C-H (Hf), 4.0- N-H (Hg).

D3- N-(2-(1*H*-benzo[*d*]imidazol-2-yl) ethyl)-2-phenylthiazol-5-amine

M.P- 194-196°C, % Yield- 62%, IR (KBr) (cm-1) - 2945 (N-H) stretch, 1662 (C-H) bending, 1563 (C=C) stretch, 1266 (C-N) Vibration. NMR- 7.2-7.5- Ar-H (Ha), 5.0-N-H (Hb), 6.8 – C-H (Hc), 7.4-8.0- Ar-H (Hd), 2.8-3.4- CH_2 (He), 4.0- N-H (Hf).

D4- N-(2-(5-nitro-1*H*-benzo[*d*]imidazol-2-yl) ethyl)-2-phenylthiazol-5-amine

M.P- 166-168°C, % Yield- 40.5%, IR (KBr) (cm-1) - 3416 (N-H) stretch, 1561 (C=C) stretch, 642 (C=C) bending, 1265 (C-N) Vibration, 2065 (C-H) bending. NMR –7.2-7.5 Ar-H (Ha), 5.0- N-H (Hb), 6.8 C-H (Hc), 7.4-

8.0 Ar-H (Hd), 2.6-3.4 CH_2 (He), 4.0 N-H (Hf).

D5- N-(3-(1*H*-benzo[*d*]imidazol-2-yl) propyl)-2-phenylthiazol-5-amine

M.P- 184-186℃, % Yield- 38.6%, IR (KBr) (cm-1) – 1649 and 1634 (C-H) bending, 1445 (C=C) stretch, 2924(C-H) Aliphatic stretch, 3290 (N-H) stretch, 1348 (C-N) Vibration. NMR- 7.1-7.5- Ar-H (Ha), 5.0- N-H (Hb), 6.8- C-H (Hc), 7.4-8.0- Ar-H (Hd), 2.0-3.3- CH_2 (He), 4.0- N-H (Hf).

D6- N-(3-(5-nitro-1*H*-benzo[*d*]imidazol-2-yl) propyl)-2-phenylthiazol-5-amine

M.P- 192-194℃, % Yield- 41%, IR (KBr) (cm-1) – 1635 (C-H) bending, 1523 (C=C) stretch, 2924 (C-H) Aliphatic stretch, 3292 (N-H) stretch, 1323 (C-N) Vibration. NMR- 7.6-8.3- Ar-H (Ha), 5.0 – N-H (Hb), 6.8 C-H (Hc), 7.4-8.0 Ar-H (Hd), 2.0-3.4 CH_2 (He), 4.0- N-H (Hf).

Pharmacological Results

The brine shrimp lethality bioassay is regarded as a helpful method for quick and informal evaluation of chemical toxicity. A laboratory lethality test for brine shrimp was carried out. Chemicals used to prepare medication solution that have been dissolved in DMSO. These outcomes were contrasted with the cytotoxic substance and the positive control (DMSO) (Bendamustin). In each test tube, 10 larval shrimp (active shrimps) were inserted.

Brine shrimp lethality bioassay

The surviving (larvae) shrimps were counted after 24 hours and lethality concentration LC50 was assessed were non-toxic at the concentration of 1000µg/ml.

- 30 active shrimps (larvae) were added into each test tube
- The surviving (larvae) shrimps were counted after 24 hours and lethality concentration LC_{50} was assessed.
- Survivors were counted after 24 hr and the percentage mortality at each vial and control was determined using the equation:

% mortality = (no. of dead nauplii/ initial no. of live nauplli) x 100

No mortality was found in the control group. An approximate linear correlation was observed when logarithm of concentrations versus percentages of mortality was plotted on graph paper. Most effective compounds were found be nontoxic in A. salina toxicity test. (LC50 >1000ug/ml).

Table No. 03

Comp.	Conc. Ppm	Mortality of shrimps			Mean mortality	Lc_{50} µg/mL
		I	II	III		
1	1000	16	16	16	54.45	814.23
	100	11	15	15	45.52	
	10	5	5	6	16.66	
	1	1	3	3	6.66	
2	1000	22	20	22	61.11	409.23
	100	14	16	16	52.22	
	10	11	12	11	36.66	
	1	6	4	6	18.88	
3	1000	24	26	23	81.11	312.68
	100	16	18	16	55.55	
	10	10	14	10	36.66	
	1	9	4	4	18.88	
4	1000	16	20	16	60	504.63
	100	14	15	15	48.88	
	10	12	14	16	46.66	
	1	9	6	5	23.33	
5	1000	16	19	19	60	681.15
	100	15	13	15	46.66	
	10	6	3	8	20	
	1	5	3	3	12.22	
	1000	18	19	18	61.11	

6	100	13	15	15	46.66	646.26
	10	6	8	6	23.33	
	1	5	4	4	14.44	
Bendamustin	1000	16	19	16	58.88	640.21
	100	18	10	15	46.66	
	10	12	13	12	41.11	
	1	5	2	3	11.11	

Control	1000	1	1≤

Positive control with DMSO has shown mortality of 2 shrimps.

No. of shrimp taken: 30

Conclusion

• IR and 1H NMR spectrum methods were used to produce and analyse derivatives. By using a brine shrimp lethality test, the cytotoxic activity of all 6 derivatives was assessed. Cytotoxicity was estimated using LC50. For the biological assessment, bendamustin was used as the standard medication. • It was discovered that substituted ortho phenylenediamine produces greater yield than unsubstituted ortho phenylenediamine. The synthesised compounds were adequately confirmed by 1H NMR,Mass and IR.

• The compounds were chosen based on the results of the molecular docking experiments and the molecules' docking scores.

• Each derivative exhibits a sizable amount of cytotoxicity. Derivative D6 outperformed the other derivatives in terms of cytotoxic activity.

• Among all the derivatives, Derivative 1 was the least cytotoxic, whereas Derivatives D2, D3, D4, and D5 had intermediate cytotoxic activity.

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References

1. Grønning T, History of Cancer, in Graham A. Colditz (ed.) the SAGE Encyclopedia of Cancer and Society, 2nd Edition. Thousand Oaks, CA: Sage Publications, 2015, 549-553.
2. Carlos P, Prostate metastatic bone cancer in an Egyptian Ptolemaic mummy, a proposed radiological diagnosis. International Journal of Paleopathology. Volume 1, Issue 2, 2011: 98–103.
3. Kumari K, Transcriptome analysis of genes associated with breast cancer cell motility in response to Artemisinin treatment.
4. Schneider K.A, the cancer genetic counseling session. In: *Counseling about cancer strategies for genetic counseling*. New York: John Wiley and sons, 2nd Ed. 2001,
5. Nishida N,Angiogenesis in Cancer, Vasc Health Risk Manag. 2006 Sep; 2(3): 213–219
6. Tricoli J, Biological and Clinical Characteristics of Adolescent and Young Adult Cancers: Acute Lymphoblastic Leukemia, Colorectal Cancer, Breast Cancer, Melanoma and Sarcoma, cancer 2016: 1017-1028.
7. Shankland K, Non-Hodgkin lymphoma, *The Lancet*, 2012, *380*(9844): 848-857.
8. Ozegowski, Bendamustin HCL for the treatment of relapsed indolent non-Hodgkin's lymphoma, Ther Clin Risk Manag. 2008 Aug; 4(4):727–732.
9. Tonelli M, Antiviral activity of benzimidazole derivatives. II. Antiviral activity of 2-phenylbenzimidazole derivatives. *Bioorganic & Medicinal Chemistry*, 2010, 18(8): 2937-2953.
10. Wright J.B, The chemistry of the benzimidazole *Chemical Reviews*, 48 (3): 397-541.
11. Wei B.Q, Weaver L.H , Ferrari A.M, Matthews B.W and Shoichet B.K , testing a flexible –receptor docking algorithm in a model binding site, Journal of Molecular biology,2004, 337 (5) : 1161-1182.
12. Cornell W.D, Journal of American Chemistry Society, 1995, 117:5179-5197.
13. Wang R, Lai L, and Wang S, Journal of Computer aided Molecular Design, 2002, 16: 11-26.

14. Huang J, Xu W, Xie H, Li S. One-Step Cyclization: Synthesis of N-Heteroalkyl-N′-tosylpiperazines. The Journal of organic chemistry. 2012 Sep 7; 77(17):7506-11.
15. Reilly S.W, Mach R.H, Pd-Catalyzed synthesis of piperazine scaffolds under aerobic and solvent-free conditions, Organic letters, 2016 Oct 21; 18(20):5272-75.
16. Gueret R, Pelinski L, Bousquet T, Sauthier M, Ferey V, Bigot A, Visible-Light-Driven Carboxylic Amine Protocol (CLAP) for the Synthesis of 2-Substituted Piperazine under Batch and Flow Conditions, Organic Letters, 2020 Jun 23; 22(13):5157-62.
17. Cochran B.M, Michael F.E, Synthesis of 2, 6-disubstituted piperazine by a diastereoselective palladium-catalyzed hydroamination reaction, Organic letters, 2008 Jan 17; 10(2):329-32.
18. Lu Z, Stahl S.S. Intramolecular Pd (II)-catalyzed aerobic oxidative amination of alkenes: synthesis of six-membered N-Heterocycles, Organic letters, 2012 Mar 2; 14(5):1234-37.
19. Montgomery T.D, Rawal VH. Palladium-catalyzed modular synthesis of substituted piperazine and related nitrogen heterocycles, Organic letters. 2016 Feb 19; 18(4):740-43.
20. Skibo E.B, Islam I, Heileman M.J, Schulz W.G, Structure-activity studies of benzimidazole-based DNA-cleaving agents, Comparison of benzimidazole, pyrrolobenzimidazole, and tetrahydropyridobenzimidazole analogs, Journal of medicinal chemistry,1994 Jan; 37(1):78-92.
21. Gerber D.E, Targeted therapies: a new generation of cancer treatments, American family physician, 2008 Feb 1; 77(3):311-19.
22. Sawyers C, Targeted cancer therapy, Nature, 2004 Nov; 432(7015):294-97.
23. Maas B, Huber C, Kramer I. Stabilität von Bendamusqtinhydrochlorid in Infusionslösungen. Pharmazie, 1994; 49(10):775-77.
24. Hesse G, Schulze W, Wachtel E, On the methodology of the determination of alkylating activities of nitrogen mustards with nitrobenzylpyridine (NBP) in biological material (author's transl). Die Pharmazie, 1981 Sep 1; 36(9):609-12.
25. Staib P, Schinkothe T, Dimski T.A, Lathan B, Boos J, Horn P.A, Voliotis D, Tesch H, Diehl V, In-vitro modulation of ara-CTP accumulation in fresh AML cells by bendamustin in comparison with fludarabine, 2-cdA and gemcitabine, In Blood 1999 Nov 15,Vol. 94, No. 10:63.
26. Rosenberg B, Vancamp L, Trosko J.E, Mansour V.H. Platinum compounds: a new class of potent antitumor agents, Nature, 1969 Apr; 222(5191):385-86.
27. Kelland L. Broadening the clinical use of platinum drug–based chemotherapy with new analogues: satrap Latin and picoplatin, Expert opinion on investigational drugs, 2007 Jul 1; 16(7):1009-21.
28. Strumberg D, Harstrick A, Doll K, Hoffmann B, Seeber S, Bendamustine hydrochloride activity against doxorubicin-resistant human breast carcinoma cell lines, Anti-cancer drugs, 1996 Jun 1; 7(4):415-21.
29. Wohlrabe K, Jungstand W, Gutsche W. Prüfung V, IMET 3393 auf die zytostatischeWirksamkeitbeioralerApplication, Pharm. 1971; 110:1045-48.
30. Preiss R, Sohr R, Matthias M, Brockmann B, HüllerH,The pharmacokinetics of bendamustin (Cytostasane) in humans, Die Pharmazie, 1985 Nov 1; 40(11):782-84.
31. Husain A, Rashid M, Mishra R, Parveen S, Shin D.S, Kumar D, Benzimidazole bearing oxadiazole and triazolo-thiadiazoles nucleus: Design and synthesis as anticancer agents, Bioorganic & medicinal chemistry letters, 2012 Sep 1; 22(17):5438-44.
32. Reck M, Haering B, Koschel G, Chemotherapie des fortgeschrittenennichtkleinzelligen und kelinzelligenBronchialkarzinomsmitBendamustin – eine Phase-II-Stusie. Pneumologie, 1998, 52:570-573.
33. Reddy T.S, Kulhari H, Reddy V.G, Bansal V, Kamal A, Shukla R, Design, synthesis and biological evaluation of 1, 3-diphenyl-1H-pyrazole derivatives containing benzimidazole skeleton as potential anticancer and apoptosis inducing agents, European journal of

medicinal chemistry, 2015 Aug 28; 101:790-805.

34. Goel R, Laxmi V, Paul K, Recent advances in development of imidazo [1, 2-a] pyrazines: synthesis, reactivity and their biological applications, Organic & Biomolecular Chemistry, 2015; 13(12):3525-55.
35. Singla P, Laxmi V, Paul K. Triazine–benzimidazole hybrids: Anticancer activity, DNA interaction and dihydrofolate reductase inhibitors, Bioorganic & medicinal chemistry, 2015 Apr 15; 23(8):1691-700.
36. El-Nassan H.B, Synthesis, antitumor activity and SAR study of novel [1, 2, 4] triazino [4, 5-a] benzimidazole derivatives, Europeanjournal of medicinal chemistry, 2012 Jul 1; 53:22-27.
37. Wang Y.T, Qin Y.J, Yang N, Zhang Y.L, Liu C.H, Zhu H.L, Synthesis, biological evaluation, and molecular docking studies of novel 1-benzene acyl-2-(1-methylindol-3-yl)-benzimidazole derivatives as potential tubulin polymerization inhibitors, European journal of medicinal chemistry, 2015 Jun 24; 99:125-37.
38. Taherian E, Khodarahmi G, Khajouei M.R, Hassanzadeh F, Dana N, Synthesis and cytotoxic evaluation of novel quinozalinone derivatives with substituted benzimidazole in position 3, Research in Pharmaceutical Sciences, 2019 Jun; 14(3):247.
39. Wang W, Kong D, Cheng H, Tan L, Zhang Z, Zhuang X, Long H, Zhou Y, Xu Y, Yang X, Ding K, New benzimidazole-2-urea derivates as tubulin inhibitors, Bioorganic& Medicinal Chemistry Letters, 2014 Sep 1; 24(17):4250-53.
40. Zuo D, Jiang X, Han M, Shen J, Lang B, Guan Q, Bai Z, Han C, Li Z, Zhang W, Wu Y, Methyl 5-[(1H-indol-3-yl) selanyl]-1H-benzoimidazol-2-ylcarbamate (M-24), a novel tubulin inhibitor, causes G2/M arrest and cell apoptosis by disrupting tubulin polymerization in human cervical and breast cancer cells, Toxicology in Vitro, 2017 Aug 1; 42:139-49.
41. Yoon Y.K, Ali M.A, Wei A.C, Shirazi A.N, Parang K, Choon T.S, Benzimidazole as new scaffold of sirtuin inhibitors: Green synthesis, in vitro studies, molecular docking analysis and evaluation of their anti-cancer properties, European journal of medicinal chemistry, 2014 Aug 18; 83:448-54.
42. Galal S.A, Hegab K.H, Hashem A.M, Youssef N.S, Synthesis and antitumor activity of novel benzimidazole-5-carboxylic acid derivatives and their transition metal complexes as topoisomerease II inhibitors, European journal of medicinal chemistry, 2010 Dec 1; 45(12):5685-91.
43. Abdel-Aziz H.A, Ghabbour H.A, Eldehna W.M, Al-Rashood S.T, Al-Rashood K.A, Fun H.K, Al-Tahhan M, Al-Dhfyan A, 2-((Benzimidazol-2-yl) thio)-1-arylethan-1-ones: Synthesis, crystal study and cancer stem cells CD133 targeting potential, European Journal of Medicinal Chemistry, 2015 Nov 2; 104:1-3.
44. Gao C, Li B, Zhang B, Sun Q, Li L, Li X, Chen C, Tan C, Liu H, Jiang Y, Synthesis and biological evaluation of benzimidazole acridine derivatives as potential DNA-binding and apoptosis-inducing agents, Bioorganic & medicinal chemistry, 2015 Apr 15; 23(8):1800-07.
45. Tahlan S, Kumar S, Kakkar S, Narasimhan B, Benzimidazole scaffolds as promising antiproliferative agents: a review, BMC chemistry, 2019 Dec; 13(1):1-6.