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# MOLECULAR DOCKING, IN SILICO PREDICTION AND IN VITRO ANTI-CANCER ACTIVITY STUDIES FOR NITROGEN RICH HYBRIDS OF DIARYL UREA-PYRIDINE ADDUCTS

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## ABSTRACT

Novel Diaryl urea-pyridine hybrids (**R1-R9**) were synthesized using Pyridine-4-carboxylic acid, 4-amino thiophenol and 4-Chloro-3-(trifluoromethyl) aniline as starting materials by a multi-step process to afford Diaryl urea derivatives (R1-R9) in good yields. The synthesized compounds were docked in the crystal structure of Raf Kinase (PDB ID: 4DBN) to get insights into structural requirements for anticancer activity. In vitro anticancer activity against MCF-7 cell line showed that compounds **R4** and **R9** were found to be the most potent (Docking score: -13.1; MIC = 17.45 µg/mL) among the synthesized molecules. All the synthesized compounds showed acceptable drug-like properties which make them suitable for further lead modification using in silico design approaches.

**Keywords: Diaryl urea, Pyridine, 4DBN, MCF-7, Molecular docking, Drug likeness**

## 1. INTRODUCTION

Cancer continues to be the most serious threat to human health in the world's most developed nations **[1]**. Globally, it is estimated that 3.5 million people die each year as a result of cancer. Chemotherapy, while intended to kill cancer cells in a patient's body, also damages normal and healthy cells, causing significant side effects and, as a result, numerous organ failure **[2]**. In 2020, 1,392,179 people in India will be diagnosed with cancer in 2020. The breast, lung, mouth, cervix,

uterus, and tongue were determined to be five most common sites of the disease, according to researcher. According to the Cancer Statistics Report, 2020, the expected incidence for men was 94.1 per 100,000 people, while for women it was 103.6 per 100,000 people **[3]**. In the United State, 1.8 million new cancer cases are predicted to be diagnosed in 2020, with 606,520 cancer fatalities, 1.9 million new cancer cases in 2021, with 606,520 cancer fatalities, and 1.9 million cases in 2022, with 609,360 cancer fatalities **[4-6]**. Because of targeted drugs, which are expressed and play critical role in cancer cells but not in normal cells, have specificity, some advances in treatment with targeted drugs like imatinib, gefitinib, and trastuzumab were expected to improve cancer cure rates while reducing severe side effect. Sorafenib is an orally administered drug that primarily targets the Ras/Raf/MEK/ ERK pathway. In the Raf/MEK/ERK signalling cascade, sorafenib inhibits wild-type B-Raf, mutant B-Raf carrying V600E, and serine-threonine kinase C-Raf **[7]**. Because many kinases are involved in signalling transduction pathway within cancer cells, they have good therapeutic targets for the identification of new anticancer agents. The B-Raf protein is involved in the activation of the Ras-Raf-MEK-ERK signalling cascade as well as normal cell development **[8]**. The diaryl urea moiety has long been considered one of the most important pharmacophores in drug design and medicinal chemistry. This is due to the urea linker's nature, in which the amine moiety is thought to be a powerful hydrogen bond donor, while the carbonyl oxygen is thought to be an excellent hydrogen bond acceptor. As a result, the urea linker was employed to fine-tune drug-like features, develop specialised drug-target interactions, and generate stable pseudo heterocycles by intermolecular hydrogen bonding. The urea linker was important in establishing HBs with the DFG motif in type II kinase inhibitors and as a hinge binding motif with the urea moiety incorporated in heterocyclic structures inside the domain of kinase inhibitor **[9]**.

In this paper, we present a design synthesis and biological evaluation of some new pyridine containing diaryl urea derivatives as anticancer agents in this study. Most type-II kinase inhibitors share the diaryl urea component of the molecule, which is extremely conserved. The N-methyl-4-picolinamide moiety that binds to the hinge region of kinase is highly mobile. The nitrogen atom in the pyridyl ring produces a hinge hydrogen bond. Based on the docking results, molecules retrieved from interactions with Raf Kinase will be synthesised by chlorination of pyridine acid derivatives, which will then be coupled

with amine to form amide, amide will then react with aminophenolic moiety to form thioether, which will then react with other aromatic amines using CDI to produce final compound. We also tested their biological evaluation using in vitro studies.

## 2. Experimental

### *2.1 Material*

The required chemicals and solvents for the synthesis were purchased from Avra Synthesis, Finar, and Spectrochem. All the chemicals were used without further purification. Precoated plates of silica gel G60 F254 (0.2 mm, Mfg. by Merck) were used for thin-layer chromatography. Spectral analysis of the synthesized compound was done with the help of FTIR-8400 (Shimadzu) using the ATR technique. The 1H NMR (400 MHz) and 13C NMR (101 MHz) spectra were recorded on the "Bruker AVANCE II Spectrometer" using DMSO-d6 as solvent and TMS as the internal reference. Mass spectra were recorded on a Jeol-JMSD 300 mass spectrometer at 70ev.

### *2.2 Synthetic Methodology*

**General procedure of 2-chloropyridine-4-carbonyl chloride (Step 1) [10-14]**

In chlorobenzene, pyridine-4-carboxylic acid (0.081mol) and sodium bromide (0.013mol) are suspended. Thionyl chloride (0.40mol) is added to such a degree after heating to 50°C. The response mixture is then heated to 85°C and stirred for 20 hours. The majority of the chlorobenzene and excess thionyl chloride are removed by distillation under decreased pressure after cooling to room temperature, and the resulting material is employed immediately in the next stage.

**4-chloropyridine-4-carboxamide derivative (Step 2)**

Triethylamine (0.0568mol) was added to a solution of 2-chloropyridine-4-carbonyl chloride (0.0284mol) in THF (50 mL) at 0° C. The amine (0.031mol) solution in THF (25 ml) was added to the reaction mixture at a pace that kept the internal temperature below 5° C. The following mixture was kept at room temperature for 5 hours before being concentrated under decreased pressure. To achieve Step-2 in R1-R9, the mixture was first diluted with water, then extracted with ethyl acetate, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. All intermediates were validated by mass spectrometry and employed without purification in the next step.

**4-(2-Aminothiophenoxy)-pyridine-4-carboxamide derivative derivative (Step 3)**

The reddish-brown mixture was added to a solution of 4-Aminothiophenol (0.0183 mol) in anhydrous DMF (15 mL) that had been treated with potassium tert-butoxide (0.0366 mol) and agitated at room temperature for 2 hours. The contents were

warmed at 80° C. for 8 hours after being treated with 4-Chloro-pyridine-4-carboxamide derivatives (Step-2 derivative) (0.0183 mol) and $K_2CO_3$ (0.009 mol). Between ethyl acetic acid derivation and water, the mixture was cooled to room temperature and separated. The natural layers were united, then washed in an immersed NaCl solution, dried over Na2SO4, and concentrated under reduced tension. The solids were then dried at 35° C for 3 hours under reduced tension to get 4-(4-Aminothiophenoxy)-pyridine-4-carboxamide derivatives (R1-R9). Mass spectroscopy was utilised to confirm all intermediates, which were then used in the experiment.

**Diaryl urea derivatives (Step 4) (R1-R9)**

Carbonyl diimidazole (CDI) was added to a solution of 4-Chloro-3-(trifluoromethyl) aniline (0.005 mol) in anhydrous at 0° C. (0.0052mol). After then, the arrangement was allowed to warm up to room temperature. It was swirled at room temperature for 1 hour. The cells were subsequently exposed to 4-(4-Aminothiophenoxy)-pyridine-4-carboxamide derivatives for 16 hours (Step-4 in R1-R9) (0.005mol). At room temperature, the resulting yellow solution was swirled. After 72 hours, it was washed down with water. With the help of ethyl acetic acid, the next fluid combination was created. The organics were mixed and dried on sodium sulphate before being concentrated under decreased pressure. To get diaryl urea derivatives as solid, the residual oil was purified using column chromatography with ethyl acetate and n-hexane as mobile phase.

**2-((4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenyl)thio)-N-(2-morpholinoethyl)isonicotinamide (R1)**

Yield (%): 56.40%, $^1$H NMR (400MHz, DMSO) δ ppm: 2.35-2.37 (t, 4H, $CH_2$), 2.52-2.54 (t, 2H, $CH_2$), 3.34-3.36 (t, 2H, $CH_2$), 3.65-3.67 (t, 4H, $CH_2$), 7.38-7.40 (m, 3H, ArH), 7.74-7.76 (d, 1H, ArH), 7.80 (s, 1H, ArH), 7.89-7.91 (m, 3H, ArH), 8.06 (s, 2H, ArH and amide), 8.43 (s, 1H, ArH), 9.12 (s, 1H, CONH), 9.25 (s, 1H, CONH), $^{13}$C NMR (DMSO) δ ppm: 37.7, 54.0, 55.8, 66.7, 117.8, 118.8, 119.4, 120.5(X2), 123.3, 122.6(X2), 123.3, 126.4(X2), 127.2, 128.5, 129.1, 129.3, 129.5, 134.3, 145.6, 149.4, 150.6, 152.9 (C=O), 153.2, 167.5 (C=O), Mass (LC-MS): m/z: 581.1$[M+H]^+$, 583.1$[M+2]^+$

**2-((4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenyl)thio)-N-(2-(diethylamino)ethyl) isonicotinamide (R2)**

Yield (%): 61.00%, $^1$H NMR (400MHz, DMSO) δ ppm: 1.02-1.04 (t, 6H, $CH_3$), 2.45-2.53 (m, 6H, $CH_2$), 3.34-3.36 (t, 2H, $CH_2$), 7.38-7.40 (m, 3H, ArH), 7.74-7.76 (d, 1H, ArH), 7.81 (s, 1H, ArH), 7.89-7.91 (m, 3H, ArH), 8.07 (s, 2H, ArH and amide),

8.44 (s, 1H, ArH), 9.12 (s, 1H, CONH), 9.25 (s, 1H, CONH), $^{13}$C NMR (DMSO) δ ppm: 13.3, 37.7, 49.6, 53.7, 117.8, 118.8, 119.3, 120.5(X2), 123.4, 122.6(X2), 123.3, 126.4(X2), 127.2, 128.7, 129.1, 129.3, 129.5, 134.4, 145.6, 149.4, 150.6, 152.9 (C=O), 153.1, 167.8 (C=O), Mass (LC-MS): m/z: 566.7[M+H]$^+$, 568.7[M+2]$^+$

**2-((4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenyl)thio)-N-ethyl-N-methyl isonicotinamide (R3)**

Yield (%): 56.40%, $^1$H NMR (400MHz, DMSO) δ ppm: 1.34-1.36 (t, 3H, $CH_3$), 3.46 (s, 3H, $CH_3$), 3.74-3.76 (t, 2H, $CH_2$), 7.38-7.40 (m, 3H, ArH), 7.74-7.76 (d, 1H, ArH), 7.82 (s, 1H, ArH), 7.88-7.91 (m, 3H, ArH), 8.07 (s, 2H, ArH and amide), 8.45 (s, 1H, ArH), 9.11 (s, 1H, CONH), 9.24 (s, 1H, CONH), $^{13}$C NMR (DMSO) δ ppm: 12.5, 36.3, 46.5, 117.8, 118.8, 119.3, 120.5(X2), 123.4, 122.6(X2), 123.3, 126.4(X2), 127.2, 128.7, 129.1, 129.3, 129.5, 134.4, 145.6, 149.4, 150.6, 152.9 (C=O), 153.1, 172.1 (C=O) Mass (LC-MS): m/z: 509.7[M+H]$^+$, 511.7[M+2]$^+$

**N-(4-(tert-butyl)phenyl)-2-((4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido) phenyl)thio) isonicotinamide (R4)**

Yield (%): 60.5%, $^1$H NMR (400MHz, DMSO) δ ppm: 1.36 (s, 9H, $CH_3$), 7.24-7.26 (d, 2H, ArH), 7.38-7.40 (m, 3H, ArH), 7.61-7.63 (d, 2H, ArH), 7.74-7.76 (d, 1H, ArH), 7.82 (s, 1H, ArH), 7.88-7.91 (m, 3H, ArH), 8.07 (s, 2H, ArH and amide), 8.45 (s, 1H, ArH), 9.11 (s, 1H, CONH), 9.24 (s, 1H, CONH), $^{13}$C NMR (DMSO) δ ppm: 31.3, 34.2, 117.8, 118.8, 119.3, 120.5(X2), 121.2(X2), 122.6(X2), 123.3, 123.4, 126.4(X2), 127.2(X2), 127.9(X2), 128.7, 129.1, 129.3, 129.5, 134.4, 145.6, 149.4, 150.6, 152.9 (C=O), 153.1, 164.7(C=O) Mass (LC-MS): m/z: 600.5[M+H]$^+$, 602.5[M+2]$^+$

**1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-((4-(piperidine-1-carbonyl)pyridin-2-yl)thio) phenyl)urea (R5)**

Yield (%): 64.20%, $^1$H NMR (400MHz, DMSO) δ ppm: 1.50-1.53 (m, 4H, piperidine ring), 1.57-1.60 (t, 2H, piperdine ring), 3.76-3.78 (t, 4H, piperidine ring), 7.38-7.40 (m, 3H, ArH), 7.74-7.76 (d, 1H, ArH), 7.82 (s, 1H, ArH), 7.88-7.91 (m, 3H, ArH), 8.07 (s, 2H, ArH and amide), 8.45 (s, 1H, ArH), 9.11 (s, 1H, CONH), 9.24 (s, 1H, CONH), $^{13}$C NMR (DMSO) δ ppm: Mass (LC-MS): 24.2, 25.4, 47.7, 117.8, 118.8, 119.3, 120.5(X2), 123.3, 126.4(X2), 127.2, 128.5, 129.1, 129.3, 129.5, 134.3, 136.2, 145.6, 149.4, 152.9(C=O), 153.1, 172.5(C=O) m/z: 535.9[M+H]$^+$, 537.8[M+2]$^+$

**1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-((4-(morpholine-4-carbonyl)pyridin-2-yl)thio) phenyl)urea (R6)**

Yield (%): 61.60%, $^1$H NMR (400MHz, DMSO) δ ppm: 3.50-3.52 (t, 2H, morpholine ring), 3.63-3.65 (t, 2H,

morpholine ring), 7.38-7.40 (m, 3H, ArH), 7.74-7.76 (d, 1H, ArH), 7.82 (s, 1H, ArH), 7.88-7.91 (m, 3H, ArH), 8.07 (s, 2H, ArH and amide), 8.45 (s, 1H, ArH), 9.11 (s, 1H, CONH), 9.24 (s, 1H, CONH), $^{13}$C NMR (DMSO) δ ppm: 46.5, 66.2, 117.8, 118.8, 119.3, 120.5(X2), 123.3, 126.4(X2), 127.2, 128.5, 129.1, 129.3, 129.5, 134.3, 136.2, 145.6, 149.4, 152.8(C=O), 153, 168.9(C=O). Mass (LC-MS): m/z: 537.8$[M+H]^+$, 539.7$[M+2]^+$

**1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-((4-(4-methylpiperazine-1-carbonyl)pyridin-2-yl)thio)phenyl)urea (R7)**

Yield (%): 59.00%, $^1$H NMR (400MHz, DMSO) δ ppm: 2.24 (s, 3H, $CH_3$), 2.27 (t, 4H, piperazine ring), 3.19-3.21 (t, 4H, piperazine ring), 7.38-7.40 (m, 3H, ArH), 7.74-7.76 (d, 1H, ArH), 7.82 (s, 1H, ArH), 7.88-7.91 (m, 3H, ArH), 8.07 (s, 2H, ArH and amide), 8.45 (s, 1H, ArH), 9.11 (s, 1H, CONH), 9.24 (s, 1H, CONH), $^{13}$C NMR (DMSO) δ ppm: 46.6, 50.1, 51.5, 117.8, 118.8, 119.3, 120.5(X2), 123.3, 126.4(X2), 127.2, 128.5, 129.1, 129.3, 129.5, 134.3, 136.2, 145.6, 149.4, 152.9 (C=O), 153.1, 168.9 (C=O). Mass (LC-MS): m/z: 550.9$[M+H]^+$, 552.8$[M+2]^+$

**2-((4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenyl)thio)-N-(2-fluoro-5-methylphenyl)isonicotinamide (R8)**

Yield (%): 55.50%, $^1$H NMR (400MHz, DMSO) δ ppm: 2.34 (s, 3H, $CH_3$), 6.94-6.95 (d, 1H, ArH), 7.09-7.11 (d, 1H, ArH), 7.38-7.40 (m, 3H, ArH), 7.70 (s, 1H, ArH), 7.74-7.76 (d, 1H, ArH), 7.82 (s, 1H, ArH), 7.88-7.91 (m, 3H, ArH), 8.07 (s, 2H, ArH and amide), 8.45 (s, 1H, ArH), 9.11 (s, 1H, CONH), 9.24 (s, 1H, CONH), $^{13}$C NMR (DMSO) δ ppm: 21.3, 113.2, 117.8, 118.5, 119.0, 119.3, 120.5(X2), 121.6, 122.9, 123.3, 126.4(X2), 127.2, 128.5, 129.1, 129.3, 129.5, 134.1, 134.3, 136.2, 145.6, 149.4, 152.9(C=O), 153.1, 155.3, 164.7(C=O). Mass (LC-MS): m/z: 575.9$[M+H]^+$, 577.8$[M+2]^+$

**2-((4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenyl)thio)-N-(2,5-difluorophenyl) isonicotinamide (R9)**

Yield (%): 50.00%, $^1$H NMR (400MHz, DMSO) 6.95-6.97 (d, 1H, ArH), 7.30-7.32 (d, 1H, ArH), 7.38-7.40 (m, 3H, ArH), 7.72 (s, 1H, ArH), 7.74-7.76 (d, 1H, ArH), 7.82 (s, 1H, ArH), 7.88-7.91 (m, 3H, ArH), 8.07 (s, 2H, ArH and amide), 8.45 (s, 1H, ArH), 9.11 (s, 1H, CONH), 9.24 (s, 1H, CONH), $^{13}$C NMR (DMSO) δ ppm: 111.7, 112.7, 113.3, 117.8, 118.8, 119.3, 120.5(X2), 120.7, 123.3, 126.4(X2), 127.2, 128.5, 129.1, 129.3, 129.5, 134.3, 136.2, 145.6, 149.4, 152.9(C=O), 153.0, 153.9, 158.7, 164.7(C=O). Mass (LC-MS): m/z: 579.9$[M+H]^+$, 581.8$[M+2]^+$

***2.3 Molecular Docking*** **[15-18]**

AutoDock Vina software was used to determine the binding mechanism and interaction of 4DBN with individual manufactured molecules. Docking was used to collect a population of probable ligand compliances and directions at the limiting location. In PyRx programming, the protein was stacked to create a PDBQT record that has a protein structure with hydrogens in every polar building. The ligands' responsibilities were all made to be rotatable. The Lamarckian Genetic Algorithm (LGA) was used to complete all computations for protein-fixed ligand-adaptable docking. A lattice box was laid out with the aspects of X: 40, Y: 40, Z: 40, and centred on X: 35.251 Y: -27.003 Z: 5.157 with an exhaustiveness of 8. The docking site on the protein target was characterised by laying out a lattice box with the aspects of X: 40, Y: 40, Z: 40, and centred on X: 35.251 Y: -27.003 Z:40.

***2.4 Anti-cancer activity*** **[19-24]**

All synthetic materials of atomic scientific grade were purchased at a low cost. HEPES [(4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), MEM-non-essential amino acid solution (100X), Fetal bovine serum (FBS), Antibiotic-Antimycotic solution, Sodium Pyruvate, Cell culture grade Dimethyl sulfoxide (DMSO), and (3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium (USA). Merck provided all atomic science-grade synthesised compounds at a reasonable price (Darmstadt, Germany). Media that is appropriate (MEM media).

**Cell Line and cell culture**

The National Center for Cell Science (NCCS), Pune, Maharashtra, India, provided a human bosom adenocarcinoma (MCF-7) cell line. MCF-7 cells were grown in MEM media with 10% FBS (foetal bovine serum), 1% non-essential amino acids, and 0.5 mL Antibiotic-Antimycotic solution (100X) (10,000 units/mL penicillin, 10,000 g/mL streptomycin, and 25 g/mL Gibco Amphotericin B). The cell lines were kept sterile at 37 degrees Celsius with 5% CO2 and 95% air, with weekly subcultures using 0.02 percent EDTA and 0.05 percent trypsin. After ingesting a high rate of nutritious agents in the cell culture medium or utilising the complete surface on which they can reproduce, cells multiplying in cultures gradually lose their proliferation rate, and cell growths slow down.

**Treatments for Compounds**

Freshly produced compounds were made in cell culture grade DMSO at a stock concentration of 100mM. For 24 hours, exponentially developing MCF-7 cells were treated with several compounds (100M). As a vehicle control, cells were treated with 0.1 percent DMSO.

***2.5 Physicochemical parameters*** **[25]**

The ADME parameters of all synthesized compounds were calculated using the SwissADME
web tool to assess their drug-likeness and bioavailability **(Table 2)**. ADME is used to describe the absorption, distribution, metabolism, excretion and toxicity of drugs. The in silico ADME profile is a useful tool to predict the pharmacological and toxicological properties of drug candidates, especially in pre-clinical stages. To improve ADME predictions, in silico models have been deployed. Use of these models has specifically been contributing to drug optimization and avoiding late-stage failures, also are important since such failures cause considerable unproductive investment of time and money.

## 3. RESULTS AND DISCUSSION

### 3.1 Chemistry

Our present research work mainly describes the synthesis of pyridine containing dirayl urea derivatives (R1-R9) and anti-cancer evaluation/studies of all the synthesized products.

The synthetic methods for the formation of the diaryl urea derivatives (R1-R9) synthesis are represented in Scheme-1. In step 1, chlorobenzene, 2-picolinic acid, and sodium bromide were suspended in Thionyl chloride to make 4-chloropicolinoyl chloride. In step 2, product was treated with respective amine derivative to yield a 4-chloropicolinoyl derivative. In final step 3, In the third step, carbonyl diimidazole (CDI) was reacted with amine derivatives to make pyridine containing diryl urea derivatives.

### 3.2 In vitro anti-cancer activity

All the synthesized compound (R1-R9) were screened for their anti-cancer activity by using available cell line (MCF-7) and checked minimum inhibitory concentration of each compound. The result showed that compound R1, R4 and R7 had showed good inhibitory action **(Table 1)**.

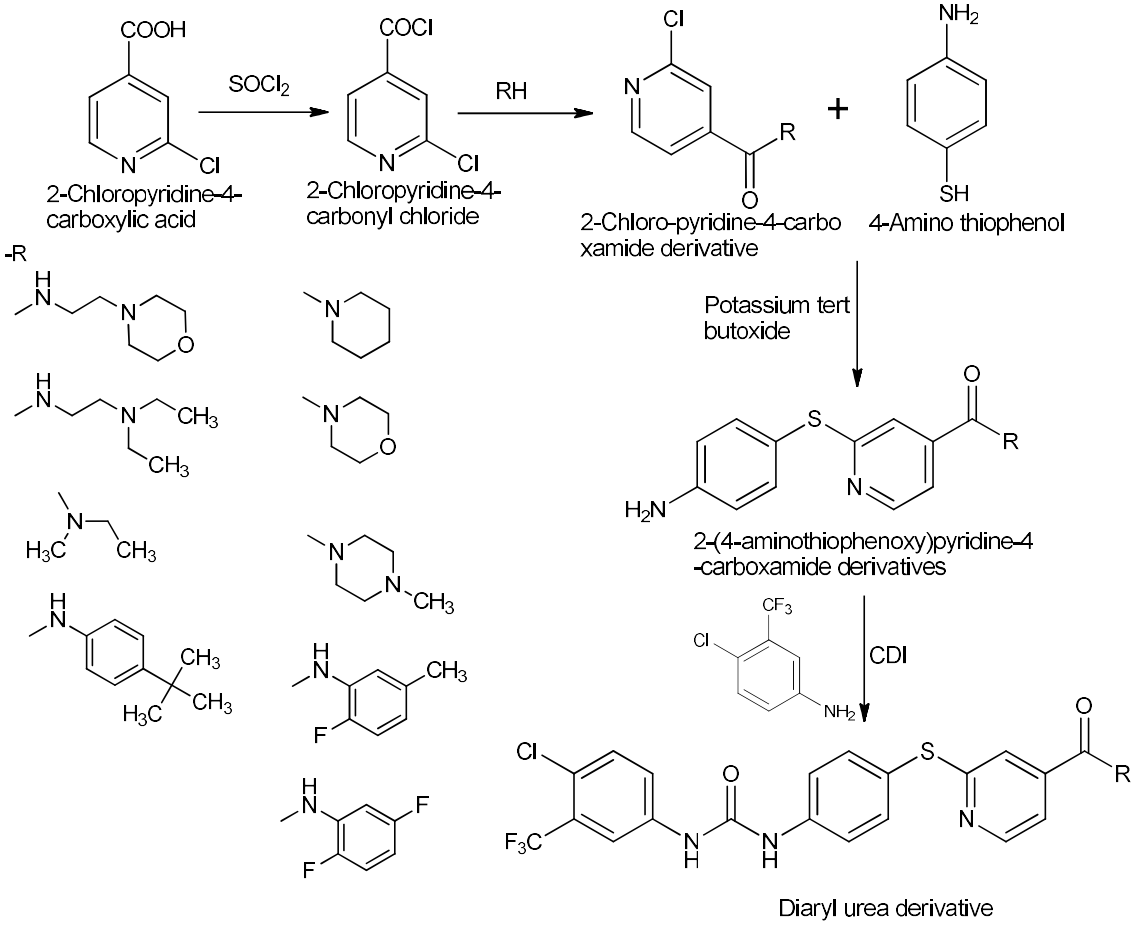
### 3.3 Drug design

In this study, we carried out the docking simulation using AutoDock Vina software in the binding site of Raf kinase crystal structure with active ligand with PDB (PDB Id: 4DBN). Most of synthesized compound have good binding site at the native substrate (4DBN). Compound showed highest docking fit score -8.2 to -13.1. Synthesized compounds made very good interactions with the surrounding residues which included H-bonds with Phe594A, Asn579A, Leu513A, Lys482A, Asp593A (R1), Asp593A, Phe582B, Phe594A, Ala480B, Leu513B, Lys482B, Thr528B (R4), Trp530B, Phe582B, Val599B (R7) **(Figure-2)**.

### 3.4 Physicochemical Properties

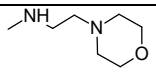
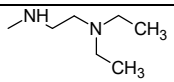
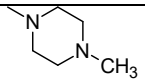
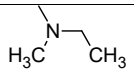
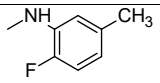
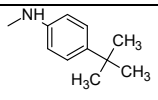
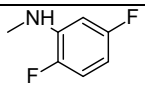
The compound was also evaluated for their physicochemical properties. All ADME parameter was checked by using SwissADME web tool to assess their drug-

likeness and bioavailability (Table 2). According to the Lipinski rule, the three compounds generated H-bond donors 5 and acceptors 10, suggesting that they are ionizable and, as a result, their solubility and absorption are adequate. The compounds' log P-values ranged from 5.5 to 9.0, and their log S-values were less than -5.5 to -8.5, indicating that they have reasonable solubility and absorbance, which is supported by the predicted intestinal absorbance **(Table 2)**. The compounds' lower TPSA values (86.80 Å²) indicated that they have better cellular internalisation characteristics.




**Scheme 1: Synthesis of Diaryl urea derivatives**

**Table 1: In vitro anti-cancer activity with Docking Score of Diaryl urea derivatives (R1-R9)**

| Compound name | R | Docking score | IC50 µM (MCF-7) | Compound name | R | Docking score | IC50 µM (MCF-7) |
|---|---|---|---|---|---|---|---|
| R1 |  | -11.5 | 21.91 | R6 |  | -11.8 | 22.10 |
| R2 |  | -8.2 | 29.97 | R7 |  | -12.0 | 23.77 |
| R3 |  | -9.7 | 22.37 | R8 |  | -9.0 | 23.75 |
| R4 |  | -13.1 | 17.45 | R9 |  | -10.7 | 17.60 |
| R5 |  | -11.2 | 29.07 | Sorafenib | - | -8.5 | 21.83 |

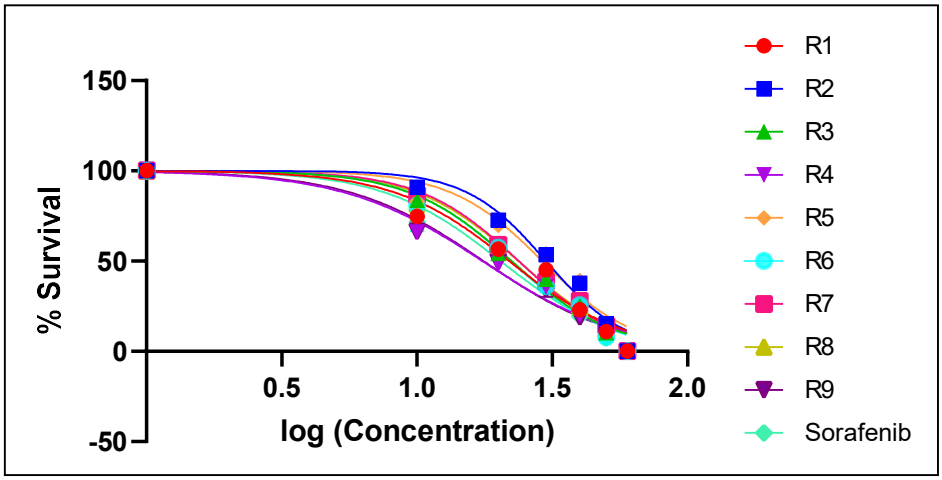
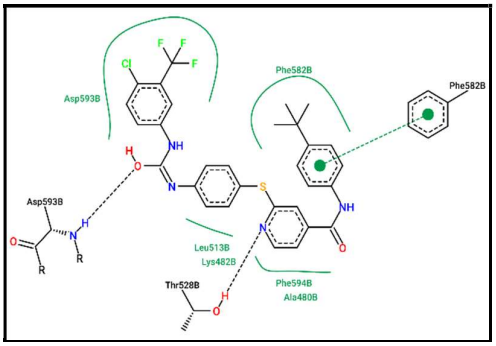
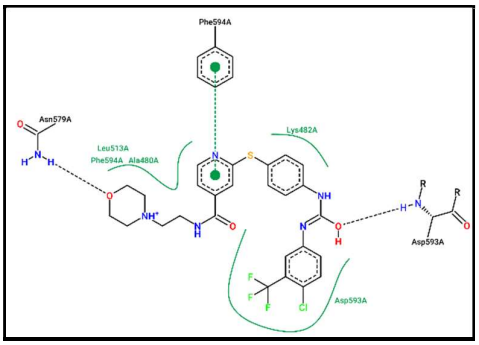


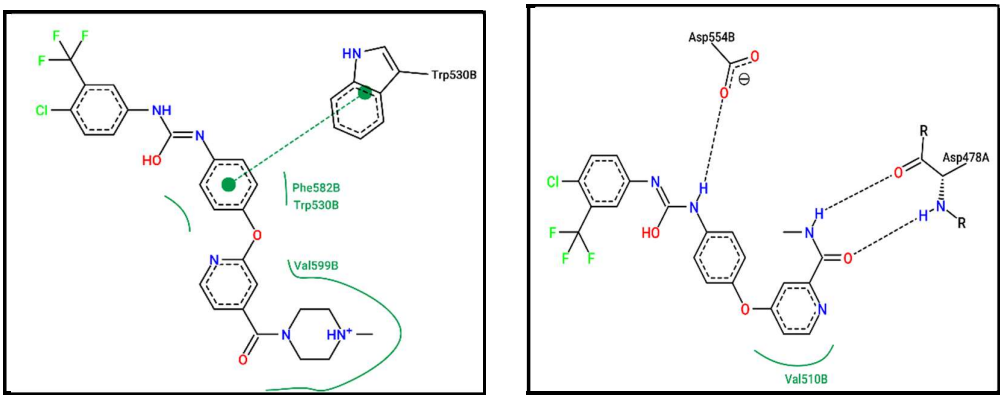

**Figure 1: %Cell survival vs log concentration graph of Sorafenib and all synthesize**




**R1**

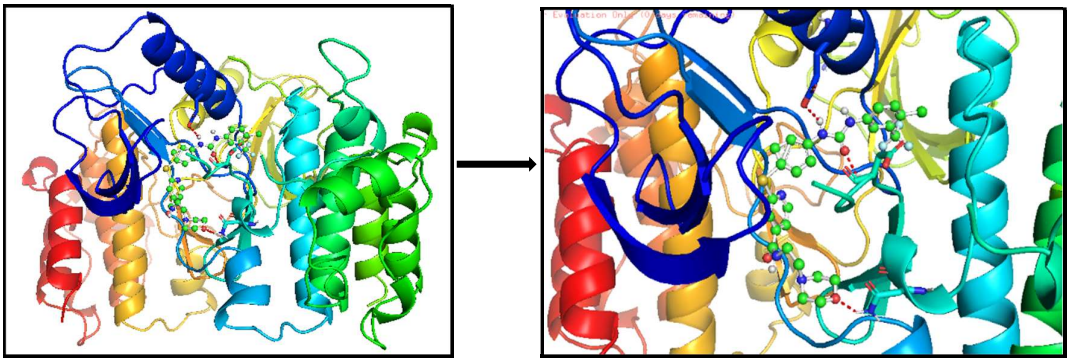



**R4**

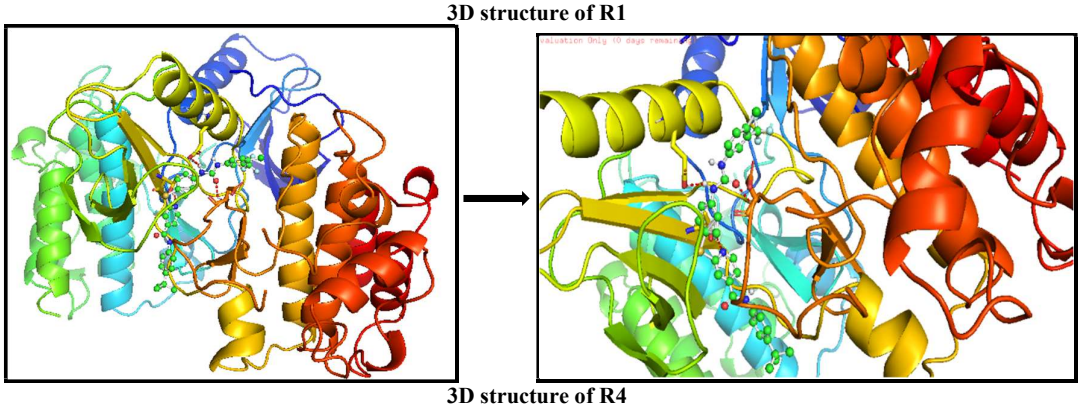



**R7** **Sorafenib**

**Figure 2: 2D views of the binding site interactions of Sorafenib all synthetic compounds R1, R4, R7**



**3D structure of R1**



**3D structure of R4**

**Figure 3: 3D views of the binding site interactions of all synthetic compounds R1 and R4 (Pink line indicates hydrogen bonding)**

**Table:2 ADME prediction of synthesized compound**

| Compound name | LogP | TPSA Å² | Log S | HBD | HBA | HIA | BBB | CYP1A2 inhibition | GIA | Lipinski filter |
|---|---|---|---|---|---|---|---|---|---|---|
| R1 | 5.611 | 120.89 | -5.68 | 3 | 8 | 86.642 | -1.485 | No | Low | Yes; 1 violation |
| R2 | 6.6206 | 111.66 | -6.17 | 3 | 7 | 82.453 | -1.486 | No | Low | Yes; 1 violation |
| R3 | 6.6409 | 99.63 | -5.98 | 2 | 6 | 82.888 | -1.428 | No | Low | Yes; 1 violation |
| R4 | 9.0988 | 108.42 | -8.20 | 3 | 6 | 79.368 | -1.397 | No | Low | No; 2 violations |
| R5 | 7.1751 | 99.63 | -6.48 | 2 | 6 | 85.257 | -1.559 | Yes | Low | No; 2 violations |
| R6 | 6.0214 | 108.86 | -5.73 | 2 | 7 | 87.044 | -1.632 | Yes | Low | Yes; 1 violation |
| R7 | 5.5777 | 86.80 | -5.47 | 2 | 8 | 84.726 | -1.719 | Yes | High | Yes; 1 violation |
| R8 | 8.24882 | 108.42 | -7.38 | 3 | 7 | 81.44 | -1.667 | No | Low | No; 2 violations |
| R9 | 8.0795 | 108.42 | -7.24 | 3 | 8 | 80.759 | -1.859 | No | Low | No; 2 violations |

**TPSA: total polar surface area, GIA: Gastrointestinal absorbance, HBD: Hydrogen bond donor, HBA: Hydrogen bond acceptor, HIA: Intestinal absorption (human), BBB: Blood Brain Barrier**

## 4. CONCLUSION

The literature-based high similar sorafenib-approved drug was submitted to structure-based virtual screening (SBVS). SBVS was completed with the use of AutoDock Vina tools. Nine compounds show solid and stable interactions in AutoDock Vina tools. Nine derivatives were created with environmentally friendly approaches. The chemical structures of the newly synthesised compounds were confirmed using physical and spectral data. These have been subjected to anticancer activity testing. The novel compounds R1, R4, and R7 surpassed the reference standard in terms of anticancer activity. The bulk of these pyridine containing diaryl urea compounds showed exceptional anticancer activity and significant binding energy using AutoDock vina methods.

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