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Synthesis and Biological Efficacy Studies of Some New Hybrid Molecules as EGFR Inhibitors

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Abstract

The epidermal growth factor receptor (EGFR) plays an important role in cell survival, growth, differentiation, tumorigenesis. Overexpression of EGFR has been observed in different types of cancers such as breast, ovarian, colon. These drugs possess many drawbacks such as Drug resistance, decreased RBC, WBC count. So, it is very important to a medicinal chemist to design such molecules which will overcome those limitations, therefore we designed and synthesized few small molecules targeting the ATP binding pocket of EGFR. In case of most of the EGFR inhibitors, 4-anilino-quinazoline is the responsible pharmacophore for the EGFR inhibitory function. On the other hand, pyrazole is another heterocyclic scaffold which is very much abundant in various types of anti-proliferative agents. By considering the above facts we designed the general molecular frame work based on the Molecular Hybridization approach i.e., a molecular framework containing both of these significant scaffolds: 4-anilinoquinazoline and pyrazole. Here in we have reported the synthesis of two compounds **(7a,7b)** with the same general molecular structure, mentioned above. There after we have checked the anti-proliferative activity of these compounds in two different types of cancer cell lines i.e. [HCT 116, PC 3]. Both these compounds have shown potent anticancer activity against these two cell lines, particularly much more effective against [HCT 116] in comparison to [PC 3]. Finally, there is a great possibility for this molecular scaffold to be a new generation EGFR inhibitor.

Keywords: Cancer, Quinazoline, Pyrazole, EGFR

Introduction

Cancer has emerged as the second leading cause of death globally and in the last year estimated deaths from cancer has reached up to 9.6 million, according to the report of World Health Organization. Globally, about 1 in 6 deaths happen due to cancer. Several cellular signaling pathways are responsible for the evolution and growth of malignant tumors. These different mechanisms create the possibility for tumors to bypass a signal transduction blockade resulting in primary or acquired resistance.(Tabernero J., 2007) Therefore, multifunctional therapeutic tools are needed for the multi-factorial nature of cancer, e.g. single molecular probe that can modulate diverse pathogenic pathways. (Antonello A et al., 2006) In the regulation of numerous cellular processes including proliferation, differentiation and survival protein kinases play significant roles. (Ishikawa T et al., 2011)

A kinase is a kind of enzyme that catalyze a process referred to as phosphorylation where phosphate groups are transferred from high-energy donor molecules, such as ATPs to specific substrates. (Kasture VS at al., 2012), (Lehninger AL et al., 2008)Kinases belong to the larger family of phosphotransferases which is a subclass of transferases.(Lehninger AL et al., 2008) Protein kinases are one of the largest groups of kinases, which regulate the activity of specific proteins. Kinases are often named after their substrates. (Kasture VS at al., 2012), (Blume-Jensen Pet al., 2001) A protein kinase is a kinase enzyme that promotes the transfer of the γ phosphate from a purine-based nucleotide triphosphate (i.e. ATP and GTP) to the protein substrate.(Kontzias A et al., 2012), (Medchemblog, 2020)

Protein kinases regulate most of the signal transduction and many other cellular processes, including metabolism, transcription and cell cycle progression. Mutations and dysregulation of protein kinases plays critical role in human disease; therefore, protein kinases are very interesting targets for therapeutic treatment in many diseases such as cancer, diabetes, inflammation, and arthritis. (Cohen P, 2002)

Protein tyrosine kinases (PTKs) catalyze the transfer of the phosphate of ATP to tyrosine residues on protein substrates.(Pytel D et al., 2009) PTKs activity is crucial in multiple cellular signaling pathways that play very important roles for critical cellular functions such as growth, proliferation, migration and apoptosis. The cells include two types of PTKs: transmembrane receptor PTKs and the nonreceptor PTKs. (Hubbard S R et al., 2000)

Epidermal growth factor receptor (EGFR):

The epidermal growth factor receptor (EGFR, also termed ErbB1, HER1) is a transmembrane receptor tyrosine kinase. EGFR is a part of the ErbB family, a four-member family of tyrosine kinase growth factor receptors that include EGFR (HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4) (Keter FK& Darkwa J., 2012) Binding of a precise set of ligands/growth factors to the extracellular domain of ErbB receptors mediates dimerization and autophosphorylation, resulting in activation of the cytoplasmic tyrosine kinasedomains which leads to downstream signaling pathways that regulate cell differentiation, cell growth, migration and apoptosis (Chilin A et al., 2010), (Yun CH et al., 2007).

EGFR has become an excellent target for chemotherapy in cancer treatment since abnormal EGFR signaling is involved in many cancers and appears to be associated with poor prognosis inhibition (Mora A et al., 2004),(Huang SM et al., 1999). The activity of the oncogenic EGFR tyrosine kinase can be inhibited by two main approaches (**Figure: 1.1**) (Pytel D et al., 2009). The first one is the use of monoclonal antibodies “mAbs” that is subjected to block the extracellular receptor domain.

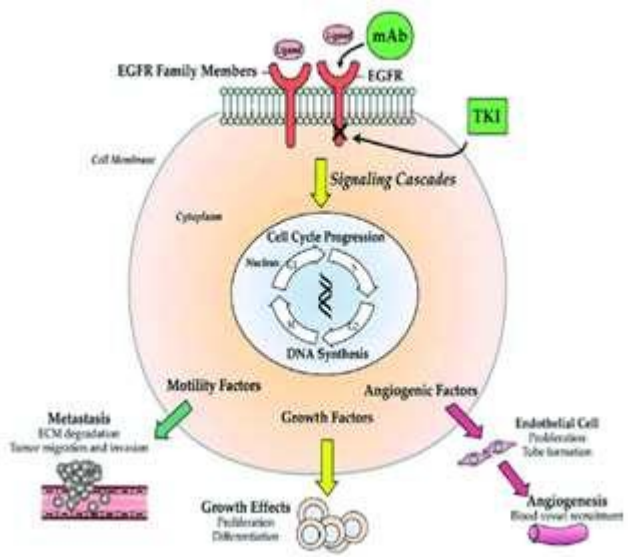
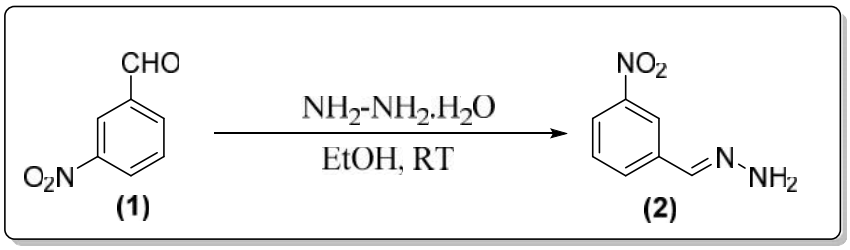


Figure 1.1: Schematic representation showing the involvement of EGFR in the transmission

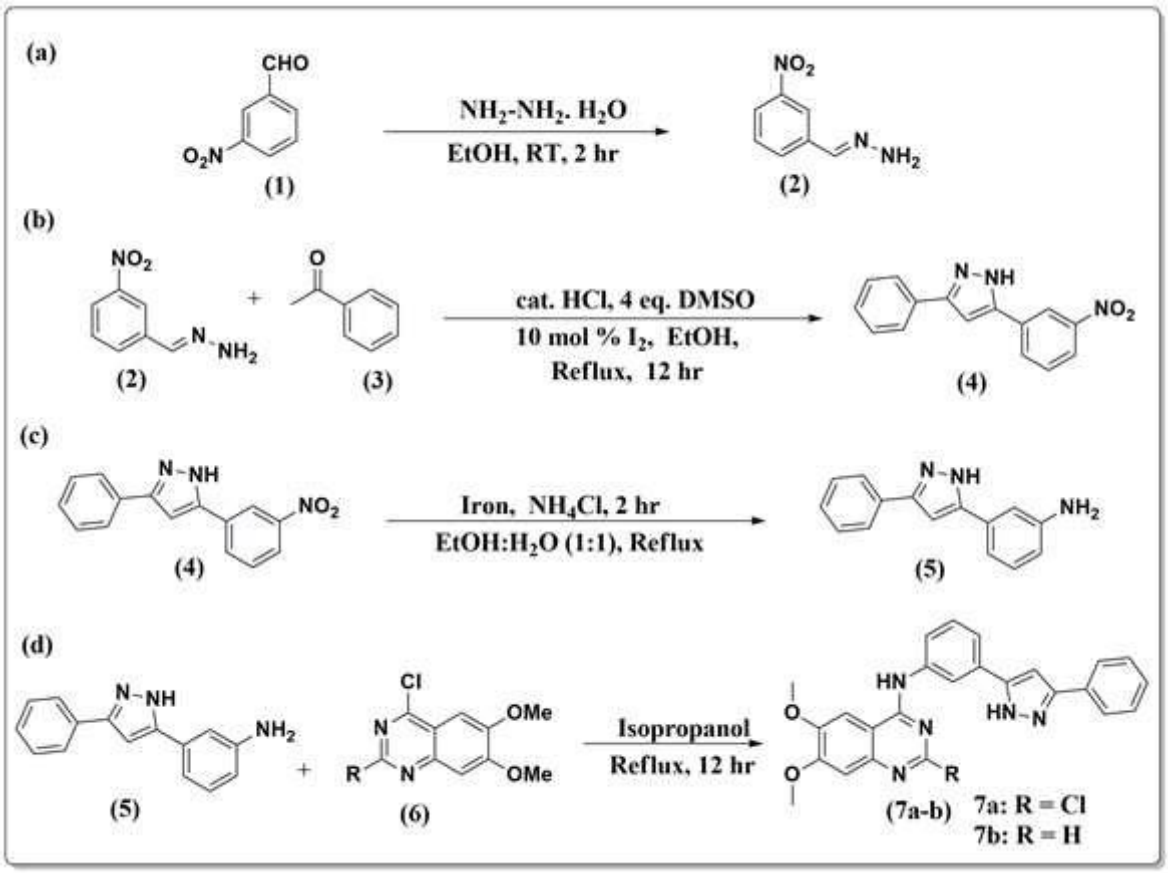
Experimental

General procedure for synthesis of (*E*)-(3-nitrobenzylidene) hydrazine (2):

To a stirred solution of hydrazine hydrate in ethanol, 1 equivalent of 3-Nitro benzaldehyde was added and the reaction mixture was stirred at room temperature until complete consumption of 3-Nitro benzaldehyde. After completion of the reaction, the solvent was evaporated and work-up was performed with ethyl acetate and water. Thereafter, the compound was purified through silica gel column chromatography and the desired product was isolated as yellow solid with 94 % yield.



General Scheme:



(a)Characterization Data for (*E*)-(3-nitrobenzylidene) hydrazine (2):

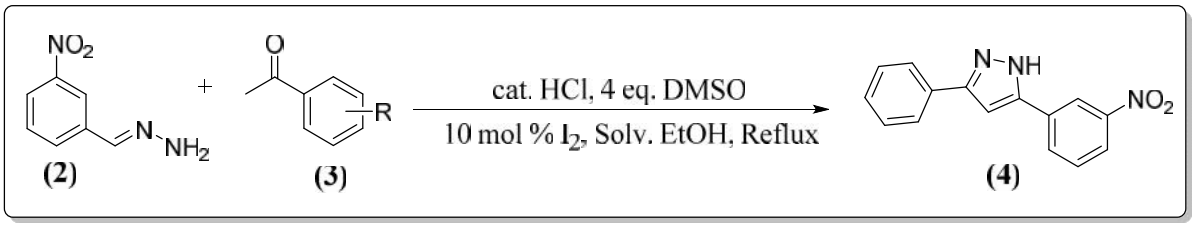
Mass (m/z): Molecular weight = 165.0538 (Calculated):$(M+H)^+$ = 166.0614 (found); Molecular formula = $C_7H_7N_3O_2$.

^{1}H (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.99 (d, J = 8 Hz, 1 H), 7.83 (d, J = 8 Hz, 1 H), 7.73 (s, 1 H), 7.56 (t, J = 8 Hz, 1 H), 7.16 (s, 2 H).

^{13}C(100 MHz, DMSO-d_6)δ148.71, 139.04, 135.36, 131.56, 130.49, 121.87, 119.32.

(b) General procedure for synthesis of 5-(3-nitrophenyl)-3-phenyl-1*H*-pyrazole 4):

To a stirred solution of acetophenone in ethanol, 1.2 equivalent of hydrazone **2** was added initially and the reaction mixture was refluxed for around one hour. Next, 10 mol% of iodine and 4 equivalent DMSO was added to the reaction mixture and the reaction was left at refluxing condition for overnight. After completion of the reaction, the solvent was evaporated and work-up was performed with ethyl acetate and water. Thereafter, the compound was purified through silica gel column chromatography and the desired product was isolated as pale yellow solid with 82 % yield.



Characterization Data for 5-(3-nitrophenyl)-3-phenyl-1*H*-pyrazole (4):

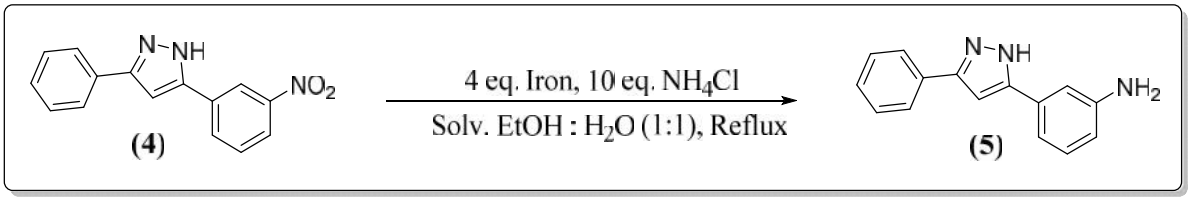
Mass (m/z): Molecular weight = 265.0851 (Calculated): $(M+H)^+$= 266.0941 (found); Molecular formula= $C_{15}H_{11}N_3O_2$

^{1}H (400 MHz, DMSO-d$_6$) δ 13.57 (s, 1 H), 8.61 (s, 1 H), 8.24 (d, *J* = 5.2 Hz, 2 H), 7.79 (d, *J* = 4.4 Hz, 3H), 7.43 (d, 3.2 Hz, 4 H).

^{13}C (100 MHz, DMSO-d$_6$) δ 149.80, 148.86, 144.45, 135.84, 138.84, 130.83, 129.56, 129.23, 128.86, 125.70, 122.52, 119.71, 100.90.

(c) General procedure for synthesis of 3-(3-phenyl-1*H*-pyrazole-5-yl) aniline (5):

To a solution of compound **4** in ethanol, same volume of water like ethanol was added and then 4 equiv iron and 10 equiv ammonium chloride were also added. This reaction mixture was then refluxed for 5-6 hours. After completion of reaction, the reaction material was passed through celite and thereafter work-up process was carried out. The purification was performed by silica gel column chromatography and the desired amine was obtained in 78 % yield as an amorphous grey colour solid.



Characterization Data for 3-(3-phenyl-1*H*-pyrazole-5-yl) aniline (5):

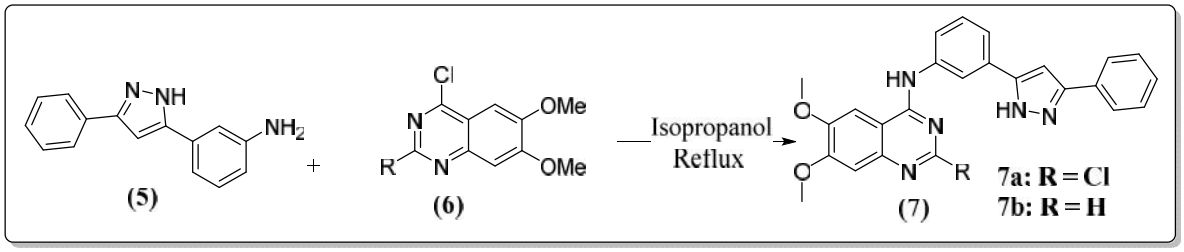
Mass (m/z): Molecular weight = 235.1109 (Calculated):$(M+H)^+$ = 236.1189 (found); Molecular formula = $C_{15}H_{13}N_3$.

^{1}H (400 MHz, DMSO-d$_6$)δ 13.20 (s, 1 H), 7.90 (s, 1 H), 7.81 (d, *J*= 8 Hz, 2 H), 7.41 (t, *J* = 8 Hz, 2 H), 7.29 (t, *J* = 8 Hz, 1 H), 7.08 (m, 2 H), 6.97 (d, *J* = 8 Hz, 1 H) , 6.56 (d, *J* = 8 Hz, 1 H), 5.12 (s, 2 H).

^{13}C (100 MHz, DMSO-d$_6$)δ 162.84, 149.46, 148.35, 129.82, 129.29, 128.16, 125.61, 122.86, 121.11, 114.31, 113.73, 112.20, 99.75.

(d) General procedure for synthesis of 2-hydro/-chloro-6,7-dimethoxy-N-(3-(3-phenyl-1H-pyrazol-5-yl)phenyl)quinazoline-4-amine (7) :

To a solution of 3-(3-phenyl-1*H*-pyrazole-5-yl) aniline**(5)** in isopropanol, 1 equiv of 2,4-dichloro/4-chloro-6,7-dimethoxy quinazoline was added and stirred at refluxing condition for overnight. After completion of the reaction, the isopropanol solvent was evaporated and the residue was dissolved Methanol-Dichloromethane mixture (in 1:1 ratio) and from this solution slurry was prepared by neutral alumina. Then the desired product was purified through neutral alumina column chromatography in 92 % yield as white solid.



Characterization Data for 2-chloro-6, 7-dimethoxy-N-(3-(3-phenyl-1H-pyrazol-5-yl) phenyl) quinazoline-4-amine (7a):

Mass (m/z): Molecular weight = 457.1306 (Calculated):$(M+H)^+$ = 458.1419 (found); Molecular formula = $C_{25}H_{20}ClN_5O_2$

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (s, 1H), 9.91 (s, 1H), 8.15 (s, 1H), 7.85 (m, 4H), 7.62 (d, *J* = 6Hz,1H); 7.43(d, *J* = 8Hz, 3H), 7.31(d, *J* = 6Hz,1H), 7.13 (d, *J* = 6Hz, 2H), 3.92 (s, 3H), 3.87 (s, 3H).

^{13}C (100 MHz, DMSO-d_6) δ 158.60, 155.48, 154.86, 149.56, 148.71, 141.96, 139.50, 130.52, 129.40, 128.66, 126.82, 125.62, 123.71, 121.77, 119.93, 116.46, 110.56, 107.79, 107.12, 102.71, 100.18, 56.78, 56.48.

Characterization Data for 6,7-dimethoxy-N-(3-(3-phenyl-1H-pyrazol-5-yl)phenyl)quinazolin-4-amine (7b):

Mass (m/z): Molecular weight = 423.1695 (Calculated):$(M+H)^+$ = 424.1698 (found); Molecular formula = $C_{25}H_{21}N_5O_2$

^{1}H NMR (400 MHz, DMSO-d_6)δ = 13.32 (s, 1 H), 9.56 (s, 1 H), 8.45 (s ,1 H), 8.18 (s,1 H), 7.85 (m, 4 H)), 7.55 (d, *J* = 8 Hz, 1 H), 7.42 (d, *J* = 8 Hz, 3 H), 7.30 (d, *J* = 6 Hz, 1 H), 7.15 (d, *J* = 12 Hz,2 H), 3.93 (s, 3 H), 3.88 (s, 3 H).

^{13}C (100 MHz, DMSO-d_6) δ156.99, 154.76, 153.45, 149.43, 147.52, 140.44, 139.76, 130.62, 129.43, 129.38, 129.33, 128.37, 125.64, 122.55, 120.94, 119.75, 115.95, 109.44, 107.69, 102.42, 100.17, 56.74, 56.31.

Molecular Docking:

To study the interaction of synthesized Pyrazole substituted Quinazoline derivatives with EGFR receptor, we performed the molecular docking studies using AUTODOCK 1.5.6 tool. For this purpose we selected crystal structure of mutated EGFR kinase domain (PDB ID: 1M17) as a receptor, compounds **7a** and **7b** compared with standard EGFR Inhibitor Erlotinib. Molecular docking was started by retrieving Crystal Structure of EGFR 696-1022 T790M Mutant from the RSC PDB database (http://www.rcsb.org/), The (PDB ID: 1M17) For the receptor refining, all non bonded atoms were removed from the receptor. The water molecules were removed from the 1M17, gasteiger charges and polar hydrogen were added to the complex by MGLTools 1.5.4. For the ligand preparation all the compounds were drawn in 2D format in marvin sketch and cleaned in 3D in the same soft ware. The energy minimization was done by online tool PRODRG server by using pdb coordinates. Docking was performed using AUTODOCK 1.5.6 software. The docking grid with a size of 60 x 58 x 60 Å was used, central coordinates X = -10.73, Y = 27.973, Z= 36.465 with 1.0 Å grid spacing in which entire macromolecules involved was covered for docking calculations. The final deviations in the receptor-ligand structure complex were regularized by energy minimization with the GROMOS96 force field using Deep View by applying 200 steps steepest descent algorithm and 200 steps conjugate gradients algorithm. All of the structures, docking pose visualization and images were generated using discovery studio visualizer software.

Cell Culture:

Human colon cancer cell line HCT116 and PC3 cell lines were obtained from ATCC. The cells were grown in DMEM (Gibco, USA) supplemented with 10% fetal bovine serum (FBS, Gibco, USA) and antibiotics (penicillin-100 µg/ml; streptomycin-50 µg/ml, Gibco). Cells were maintained in the incubator at 37 ^{o}C, in 95% air, 5% CO_2. (Kumar V et al., 2013)

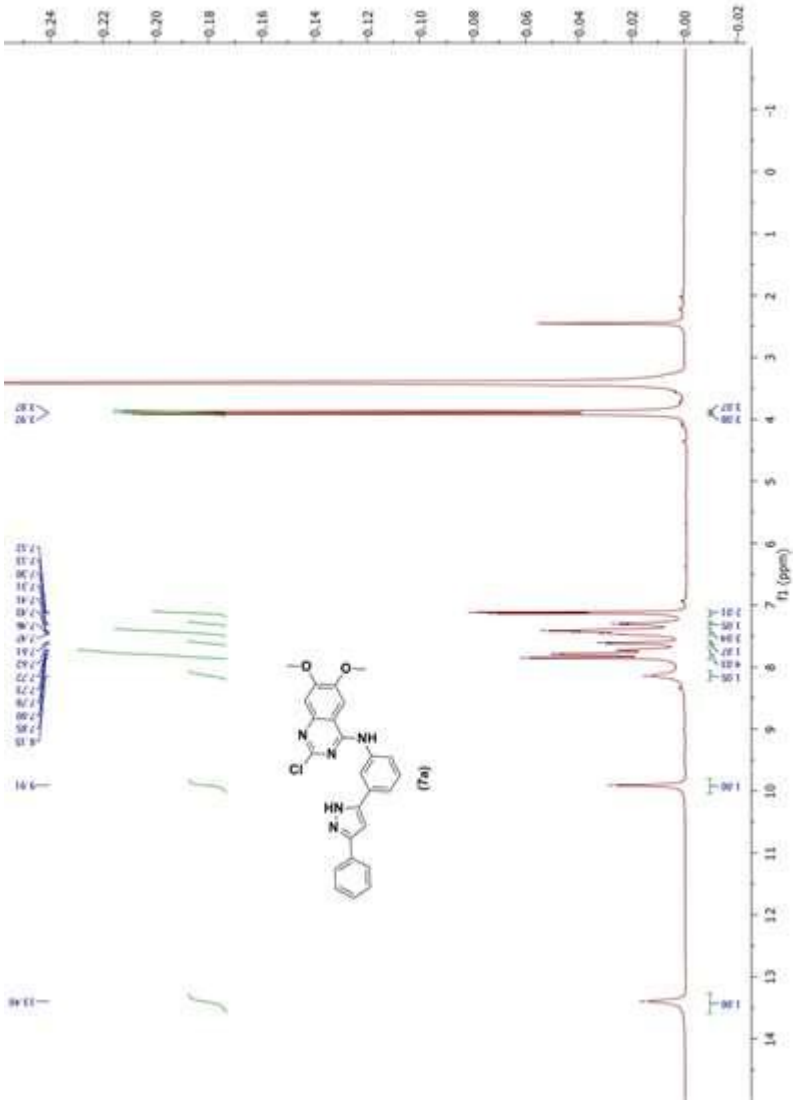
MTT Assay:

To determined the cell growth inhibition by compound **7a, 7b** was performed using the 3-(4, 5-dimethylthiazol-2-yl)-2, 5- diphenyltetrazolium bromide (MTT, Sigma-Aldrich) assay. Briefly, HCT116 and PC3 cells were seeded in 96-well plates at a density of 1×10^3 cells per well at 37 °C and treated with compound **7a, 7b** and doxorubicin for 24h. 20 µl of MTT solution [5 mg/ml 1Xphosphate-buffered saline (PBS)] was added to each well of a 96- well culture plate and again incubated continuously at 37 °C for a period of 4 h. All media were removed from wells and 100 µl of DMSO (Sigma-Aldrich) was added to each well and absorbance was measured at 550 nm (EMax Precision MicroPlate Reader, Molecular Devices, USA). Data were collected from three separate experiments and the percentage of compound **7a, 7b** and Doxorubicin induced cell growth inhibition was determined by comparison to relative to untreated control cells.(Çalışkan B et al., 2013), (Gökhan-Kelekçi N et al., 2009).

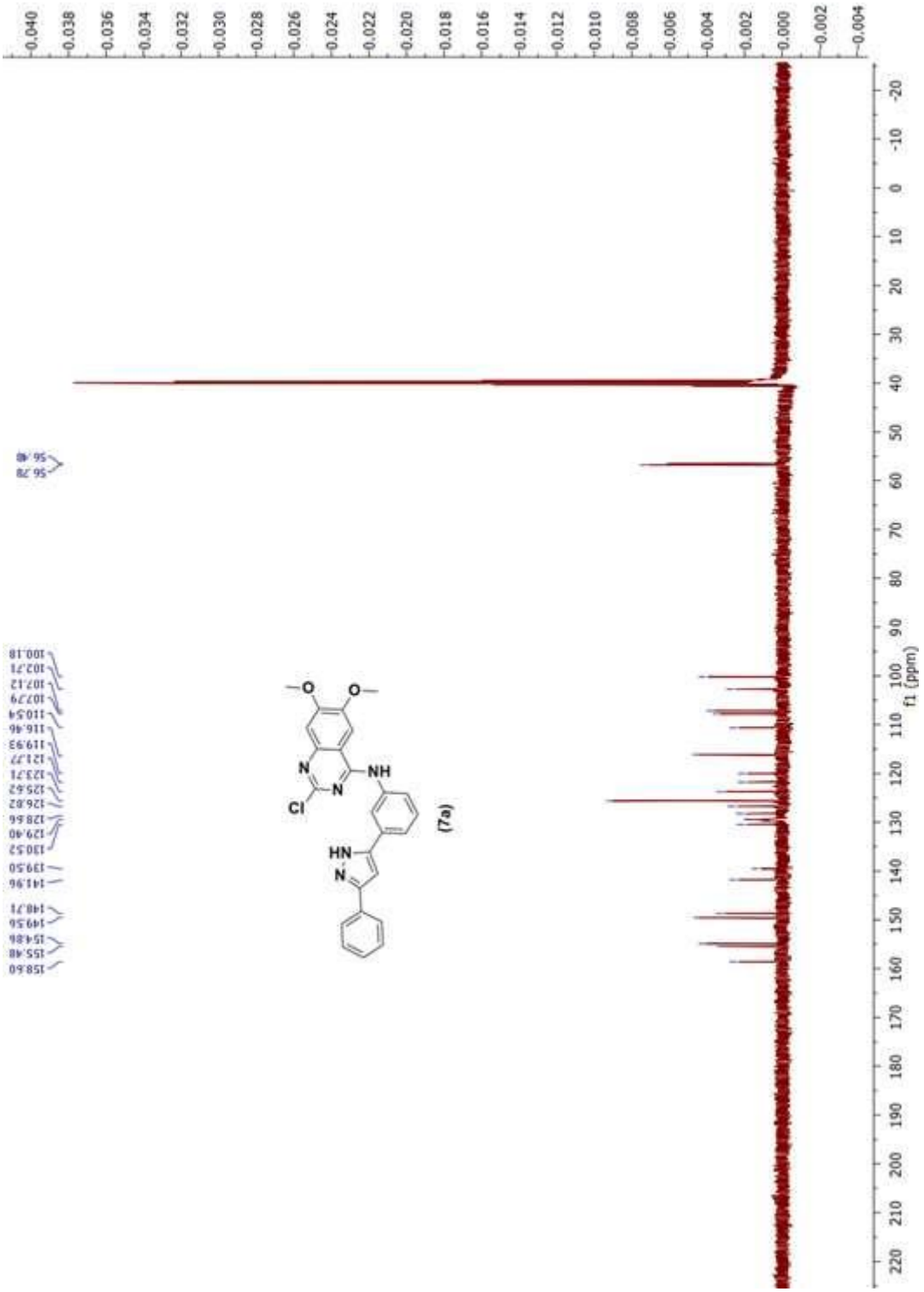
Results and Discussion

To reach our goal, the synthesis was started using 3-Nitrobenzaldehyde **(1)** as starting material in the presence of hydrazine monohydrade, ethanol as a solvent at RT. Then hydrazine **(2)** was converted into nitropyrazole **(4)** in the presence of DMSO, Iodine, catalytic amount of HCl, and ethanol as solvent. Now the nitro group of Pyrazolewas converted to corresponding amine **(5)** in the presence of Iron powder, Ammonium chloride, Ethanol, water used as solvent. The amine group of compound **(5)** was further coupled with different Quinazolines **(6)** to obtain the respective final molecules in moderate to good yield **(7a, 7b).**

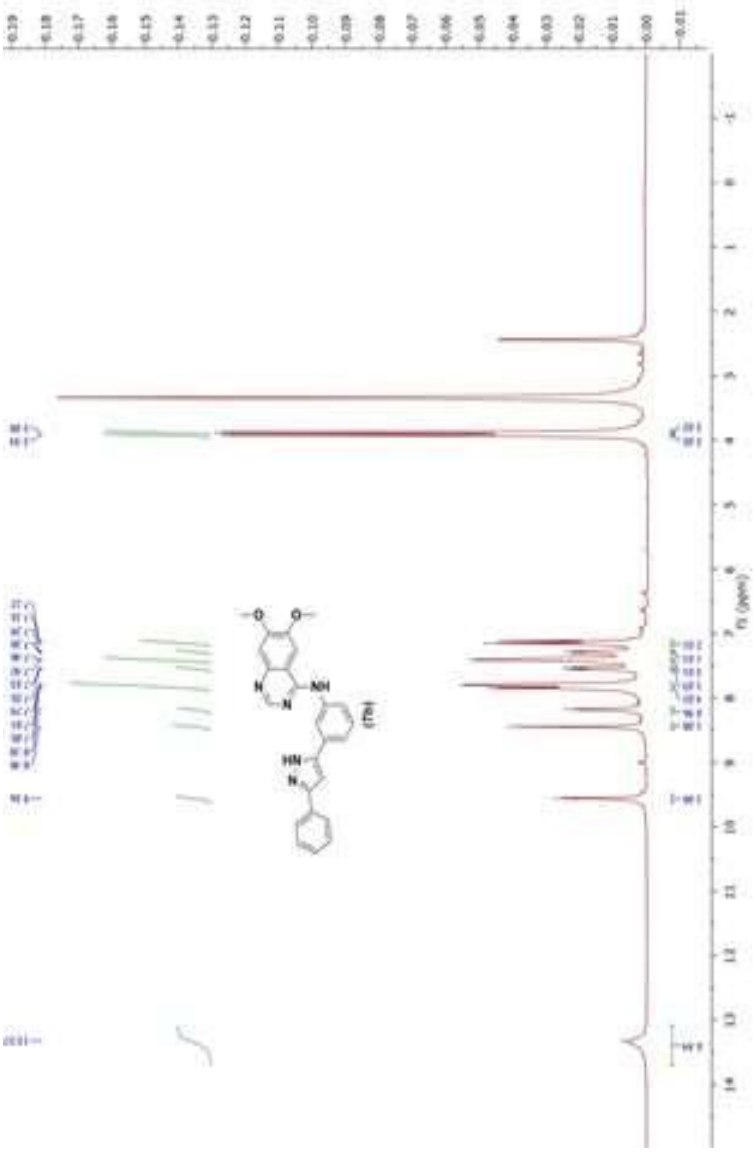
^{1}H NMR spectra of 2-chloro-6, 7-dimethoxy-N-(3-(3-phenyl-1H-pyrazol-5-yl) phenyl) quinazoline-4-amine (7a):



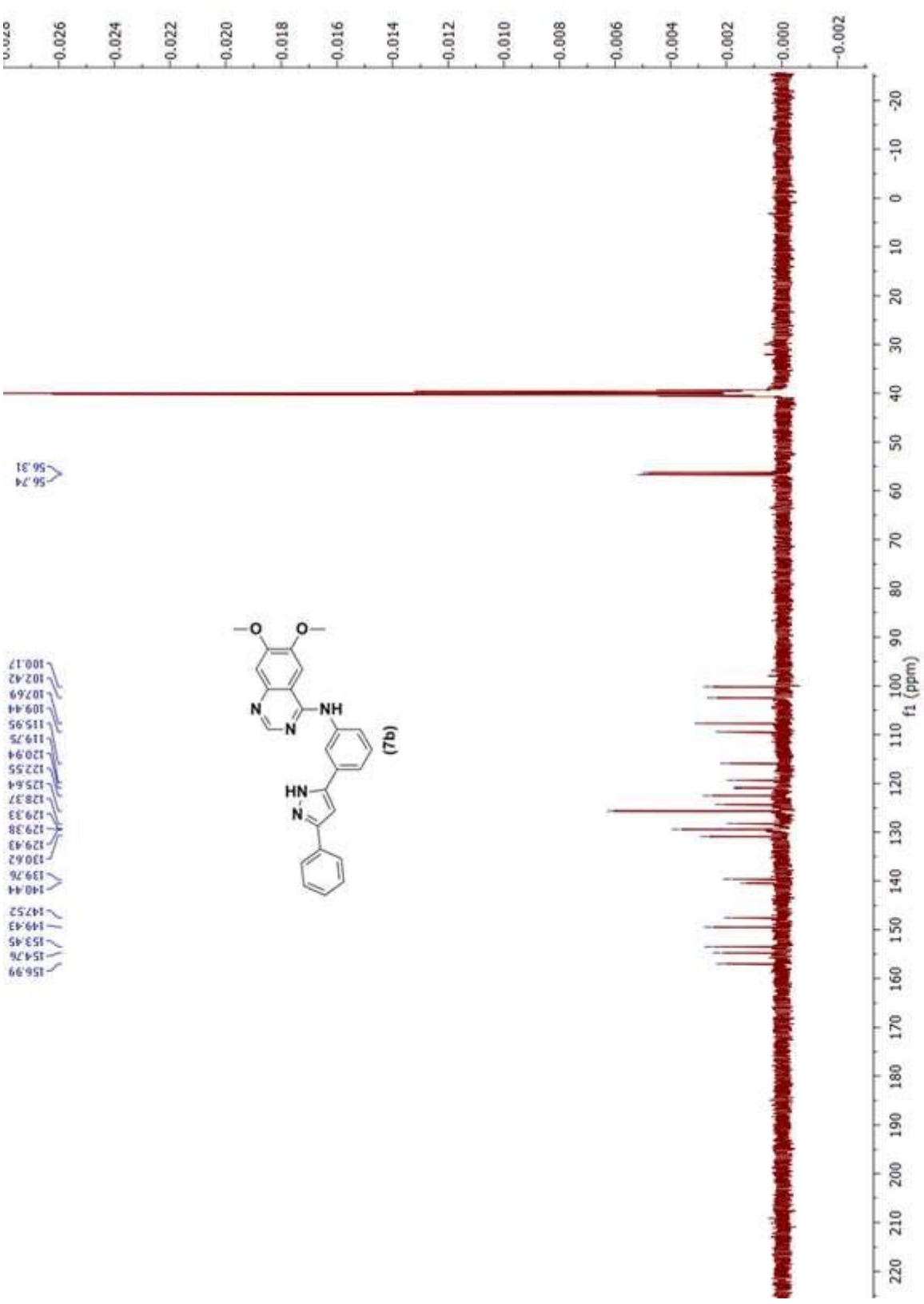
^{13}C NMR spectra of 2-chloro-6, 7-dimethoxy-N-(3-(3-phenyl-1H-pyrazol-5-yl) phenyl) uinazoline-4-amine (7a):



^{1}H NMR spectra of 6,7-dimethoxy-N-(3-(3-phenyl-1H-pyrazol-5-yl)phenyl)quinazolin-4-amine (7b):



^{13}C NMR spectra of 6,7-dimethoxy-N-(3-(3-phenyl-1H-pyrazol-5-yl)phenyl)quinazolin-4- amine (7b):



The docking results suggested that the designed new hybrid molecule (**7a**) goes and binds with ATP binding pocket of EGFR tyrosine kinase (PDBID:1M17) and showing 2 hydrogen bonding interactions with Met 793,Cys 797, vanderwaal interactions with Gly 796 and Leu 718. The compound (**7b**) is also showing Hydrogen bonding interactions with Lys 716, amide–π stacking with Gly 796, Met 793 and also π-σ interactions with Leu718.Compound **7a**, and**7b** having the binding energies -7.78, -6.4 respectively. All the docking parameters were placed in **Table 1.**

Table 1: Docking Results of Synthesized Compounds

S.No	First conformation information	7a	7b
1	Binding energy	-7.78	-6.42
2	Ligand efficiency	-0.24	-0.23
3	Inhibitory constant (µM)	10.97	19.85
4	Intermolenergy	-9.57	-8.2
5	Desolvationenergy	-9.64	-8.02
6	Electrostatic energy	-0.06	-0.18
7	Totalinternal energy	-1.29	-1.23
8	Torsional energy	1.79	1.79
9	Unbound energy	-1.29	-1.23
10	refRMS	56.37	54.81

Among all compounds, **7a** having best binding efficiency with binding energy -7.78 and it shows inhibitory constant 10.97 µM. The binding mode and key interactions of the molecules **7a, 7b**were placed in the following figures **(4.1, 4.2).**

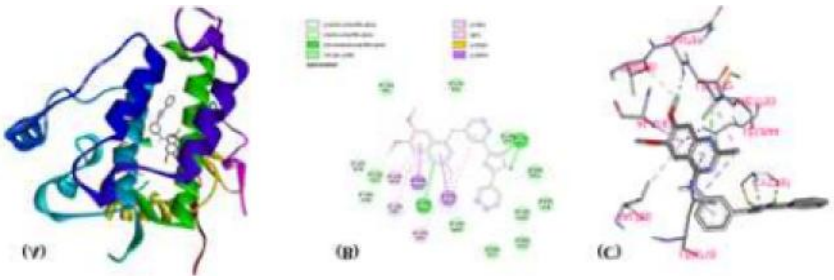


Figure 4.1: (A) Ribbon representation of the EGFR kinase protien (PDB ID 1M17) along with compound **7a** (B) two-dimensional (2D) and (C) Three dimensional (3D) representation of ligand receptor interactions of compound **7a.**

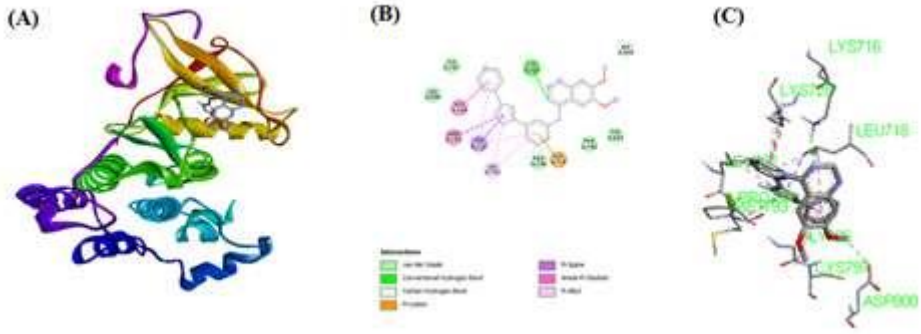


Figure 4.2: (A) Ribbon representation of the EGFR kinase protien (PDB ID 1M17) along with compound **7b** (B) Two-dimensional (2D) and (C) Three dimensional (3D) representation of ligand receptor interactions of compound **7b.**

Biological Data:

Table 2: IC_{50} values of compounds (**7a-7b**) against HCT116, PC-3 in Micromolar.

S.no	Name	R	HCT116	PC3
1	7a	Cl	8.42 µM	10 µM
2	7b	H	5.74 µM	8.14 µM
3	Doxorubucin	-	4 µM	3.25 µM

Conclusion

The present study has outlined the design and synthesis of Quinazoline-pyrazole hybrid molecules. The synthetic methodology is easy and allows large substrate variations with high yields. A small set of molecules were synthesized and fully characterized by using NMR, MASS. The binding site and interactions of the synthesized compounds with the receptor was performed by molecular docking studies using Auto Dock tools. The preliminary cell viability assay (MTT assay) was performed against human colorectal cancer cell line (HCT 116), human prostate cancer cell line (PC 3). In near future we will synthesize more compounds and explore the structural activity relationship (SAR) based on cell viability assay results and further extended our studies to elucidate mechanism of action of the best compound.

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