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Article *in* Research Journal of Pharmacy and Technology · August 2017

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RESEARCH ARTICLE

Design, Synthesis and *In Silico* Molecular Docking Study of N-carbamoyl-6-oxo-1-phenyl-1, 6-dihydropyridine-3-carboxamide derivatives as Fibroblast growth factor 1 inhibitor

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ABSTRACT:
A novel series of N-carbamoyl-6-oxo-1-phenyl-1, 6-dihydropyridine-3-carboxamide derivatives (A1-A6) were synthesized by various substitution and their structures were confirmed by spectral and elemental analyses. The cytotoxic activity of the newly synthesized compounds was docked against fibroblast growth factor 1 (FGF1). These FGFR cascades play crucial roles in tumor cell proliferation, angiogenesis, migration, and survival. FGFRs were also identified in a variety of human cancers such as ovarian cancer, myeloproliferative syndromes, lymphomas, prostate and breast cancers as well as other malignant diseases. The molecular docking study was used for confirming their interaction with fibroblast growth factor 1. Thorough *in silico* molecular docking study, the result showed that all synthesized derivatives (A1-A6) have low binding energy (Table 1) and have good affinity toward their active pocket. Thus the synthesized derivatives considered as good anti cancer agents.

KEYWORDS: 2-pyridone derivatives, Fibroblast growth factor 1, Molecular docking methodology.

INTRODUCTION:

Aromatic heterocyclic compounds represent an important group of compounds due to their biological and medical applications. The six-member heterocyclic rings containing nitrogen (e.g., pyridine, pyridone, pyrimidine, piperidine and piperazine) are used in medicine since they possess certain pharmacological properties. Among them, 2-pyridone compounds are particularly significant (Figure 1). 2-Pyridone derivatives are especially interesting because the 2-pyridone structure is present in many compounds of natural origin [1].

Received on 18.04.2017 Modified on 23.07.2017
Accepted on 19.08.2017
Research J. Pharm. and Tech. 2017; 10(8): 2527-2534.
DOI: 10.5958/0974-360X.2017.00447.4

Due to a variety of pharmacological properties, the 2-pyridone structure is important in the pharmaceutical industry [2]. Many medications contain 2-pyridone structure: cardiotonics (milrinone and amrinone) used for the treatment of heart failure [3]; and antibiotics (pilicides and curlicides) which treat bacterial infections caused by Gram-negative bacteria [3,4].

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. The majority of cancers, some 90–95% of cases, are due to environmental factors. The remaining 5–10% are due to inherited genetics, Environmental, as used by cancer researchers, means any cause that is not inherited genetically, such as lifestyle, economic and behavioral factors and not merely pollution [5, 6]

Ovarian cancer is a cancer that forms in an ovary. It results in abnormal cells that have the ability to invade or spread to other parts of the body. When this process begins, there may be no or only vague symptoms. Symptoms become more noticeable as the cancer progresses. These symptoms may include bloating, pelvic pain, abdominal swelling, and loss of appetite, among others. Common areas to which the cancer may spread include the lining of the abdomen, lining of the bowel and bladder, lymph nodes, lungs, and liver [7].

Use of fertility medication may contribute to borderline ovarian tumor formation, but the link between the two is disputed and difficult to study [8]. Fertility drugs may be associated with a higher risk of borderline tumors. Those who have been treated for infertility but remain nulliparous are at higher risk for epithelial ovarian cancer; however, those who are successfully treated for infertility and subsequently give birth are at no higher risk [9]. This may be due to shedding of precancerous cells during pregnancy but the cause remains unclear. The risk factor may instead be infertility itself, not the treatment [10]. Tyrosine kinase inhibitors are another investigational drug class that may have applications in ovarian cancer.

The protein encoded by this gene is a member of the fibroblast growth factor (FGF) family. FGF family members possess broad mitogenic and cell survival activities, and are involved in a variety of biological processes, including embryonic development, cell growth, morphogenesis, tissue repair, tumor growth and invasion. This protein functions as a modifier of endothelial cell migration and proliferation, as well as an angiogenic factor [11, 12]. It acts as a mitogen for a variety of mesoderm- and neuroectoderm-derived cells in vitro, thus is thought to be involved in organogenesis. Multiple alternatively spliced variants encoding different isoforms have been described [13].

The fibroblast growth factor receptor (FGFR) family includes four highly conserved receptor tyrosine kinases: FGFR 1–4. Upon ligand binding, FGFRs activate an array of downstream signaling pathways, such as the mitogen activated protein kinase (MAPK) and the phosphoinositide-3-kinase (PI3K)/Akt pathways [14, 15]. The combination of knockdown studies and pharmaceutical inhibition in preclinical models demonstrates that FGFRs are attractive targets for therapeutic intervention in cancer. Multiple FGFR inhibitors with various structural skeletons have been designed, synthesized, and evaluated [16].

In addition, the inhibitory activity of the target compounds against epidermal growth factor receptor tyrosine kinase (EGFR-TK) was evaluated. Results indicated the ability of the target compounds to inhibit EGFR-TK with half maximal inhibitory concentrations (IC50) in the range of 4.18-35.88μM. Furthermore, The most active compounds 12g, 12c and 12d were assayed against Fibroblast Growth Factor Receptor (FGFR), Insulin Receptor (IR) and Vascular Endothelial Growth Factor Receptor (VEGFR). The activity of the reported compounds warrants further optimization as novel members in cancer treatment protocols [16, 17].

Fibroblast growth factor receptor 1 (FGFR1) a tyrosine kinase receptor, plays important roles in angiogenesis, embryonic development, cell proliferation, cell differentiation, and wound healing. The FGFR isoforms and their receptors (FGFRs) considered as a potential targets and under intense research to design potential anticancer agents [18]. Fibroblast growth factors are key proteins in many intercellular signaling networks. They normally remain attached to the extracellular matrix, which confers on them a considerable stability [19]. The unrestrained accumulation of fibroblast growth factors in the extracellular milieu, either due to uncontrolled synthesis or enzymatic release, contributes to the pathology of many diseases. Consequently, the neutralization of improperly mobilized fibroblast growth factors is of clear therapeutic interest [19, 20]. In pursuing described rules to identify potential inhibitors of these proteins, 2-pyridone was singled out as an inhibitor of fibroblast growth factors [21]. 2-pyridone was used as a lead to identify additional compounds with better inhibitory characteristics generating a new chemical class of fibroblast growth factor inhibitors that includes the agent responsible for alkaptonuria. It was shown that this class of inhibitors may employ two different mechanisms to interfere with the assembly of the signaling complexes that trigger fibroblast growth factor-driven mitogenesis. In addition, we obtained evidence from in vivo disease models that this group of inhibitors may be of interest to treat cancer and angiogenesis-dependent diseases [20, 21, 22].

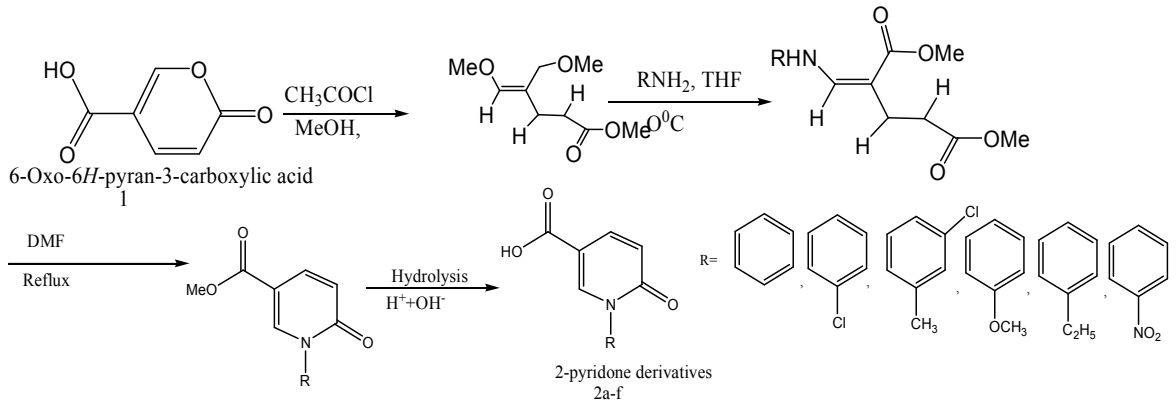
Cancer chemotherapy has been one of the major medical advances in the last few decades. However, the drugs used for this therapy have a narrow therapeutic index, and often the responses produced are only just palliative as well as unpredictable. In contrast, targeted therapy that has been introduced in recent years is directed against cancer-specific molecules and signaling pathways and thus has more limited nonspecific toxicities. Tyrosine kinases are an especially important target because they play an important role in the modulation of growth factor signaling [22, 23].

Tyrosine kinase inhibitors are another investigational drug class that may have applications in ovarian cancer. The protein encoded by this gene is a member of

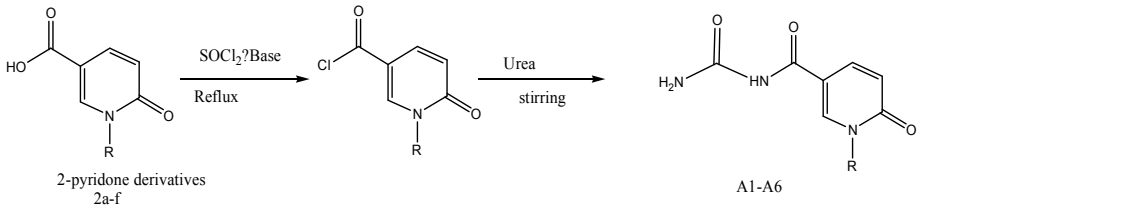
the fibroblast growth factor (FGF) family. FGF family members possess broad mitogenic and cell survival activities, and are involved in a variety of biological processes, including embryonic development, cell growth, morphogenesis, tissue repair, tumor growth and invasion. This protein functions as a modifier of endothelial cell migration and proliferation, as well as an angiogenic factor. It acts as a mitogen for a variety of mesoderm- and neuroectoderm-derived cells in vitro, thus is thought to be involved in organogenesis [23, 24]. In normal tissue, basic fibroblast growth factor is present in basement membranes and in the sub-endothelial extracellular matrix of blood vessels. It stays membrane-bound as long as there is no signal peptide [25].

Scheme:

STEP -I



STEP-II



N-carbamoyl-6-oxo-1-phenyl-1, 6-dihydropyridine-3-carboxy derivatives

MATERIALS AND METHOD:

General:

All the chemicals were purchased from Sigma Aldrich and used without purification. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker advance II 400 instrument, using deuterated DMSO as a solvent and tetramethylsilane (TMS) as internal standard (δ = 0). IR spectra were obtained using a Schimadzu 400 FTIR spectrophotometer, using potassium bromide disks, scanning from 600 to 4000 cm^{-1}. Low resolution mass spectra were recorded on a Waters, Q-TOF Micromass(LC-MS) instrument under ESI conditions.

The elemental analysis was done by Thermo Finnigan instrument with Calibration method: K Factors. Analytical thin layer chromatography analysis was conducted on aluminum backed precoated silica gel plates.

Step-I:

General procedure for the preparation of 2-pyridones derivatives (2a-f): A coumalic acid (3.00 g, 21.41 mmol) was reacted with Acetyl chloride (2.83 mL, 21.41 mmol) was dropwise in MeOH (30 mL) over 10 min at 0°C. The reaction mixture was refluxed for 12 hrs in oil bath, cooled to room temperature followed by concentration yield a mixture of methyl 5-methoxy-4-(methoxymethyl)pent-4-enoate (1), which was treated by the reaction of aniline derivatives(1.10 mmol) in DMF (5 mL) and it was refluxed for cyclization. After cyclization it was hydrolysed with acidic water and heats the mixture. The filtrate was concentrated *in* lyophilizer to yield a solid product which was recrystalized in ether/*n* hexane [26].

1,6-dihydro-6-oxo-1-phenylpyridine-3-carboxylic acid (2a): Yield 70%, yellowish solid, mp 162-164 oC; **^{1}H NMR** (400 MHz, DMSO): δ 6.42(d, 1H), 6.96 (m, 1H), 7.24(d, 1H), 7.64(d, 1H), 8.15 (d, 1H), 11.10(d, 1H); **^{13}C NMR** (400 MHz, DMSO): δ 103.4, 119.5, 121.5, 129.5, 140.1, 161.2, 165.7; IR (KBr) 3410, 3290, 3060,2930,1707, 1650, 720 cm $^{-1}$; MS: m/z 215.3 (M+).

1-(4-chlorophenyl)-1,6-dihydro-6-oxopyridine-3-carboxylic acid (2b): Yield 82%, brown semisolid; **^{1}H NMR** (400 MHz, DMSO): δ 6.43 (d, 1H), 6.95 (d, 1H), 7.25 (d, 2H), 7.59 (d, 2H), 8.26 (s, 1H), 11.10(d, 1H); **^{13}C NMR** (400 MHz, DMSO): δ 103.5, 118.7, 123.7,130.4, 139.1, , 160.2, 166.4; IR (KBr) 3440,3280, 3020, 2950, 1710, 1690, 1650cm $^{-1}$; MS: m/z 294.2 (M+).

1-(4-ethylphenyl)-1,6-dihydro-6-oxopyridine-3-carboxylic acid (2c): Yield 90%, light brown solid, mp 140-144 oC; **^{1}H NMR**(400 MHz, DMSO): δ 1.24 (m, 5H), 2.60 (m, 1H), 6.43 (d, 1H), 6.95 (d, 1H), 7.10 (m, 2H), 7.60 (m, *J* 2H), 8.20(s, 1H), 11.0(d, 1H); **^{13}C NMR** (400 MHz, DMSO): δ 32.5, 103.4, 119.0, 121.5, 130.3, 128.6, 139.0, 143.0, 161.2, 166.0; IR (KBr) 3390, 3010, 2890, 2940, 1700, 1670, 1610 cm^{-1}; **MS:** m/z 227.09 (M+).

1-(2-chloro-4-methylphenyl)-1,6-dihydro-6-oxopyridine-3-carboxylic acid (2d): Yield 70%, yellowish solid, mp 156-158 ^{o}C; **^{1}H NMR** (400 MHz, DMSO): δ 35 (s, 3H), 6.42 (d, 1H), 6.69 (m, 1H), 7.01(d, 2H), 7.50(d, 2H), 8.26 (s, 1H), 11.04 (d, 1H); **^{13}C NMR** (400 MHz, DMSO): δ 23.9, 103.4, 119.0, 122.0, 130.2, 135.4, 161.3, 166.0; IR (KBr) 3290,3033, 2890, 2910, 1720, 1690, 1600, 720 cm^{-1}; **MS:** m/z 263.04 (M+).

1,6-dihydro-1-(4-methoxyphenyl)-6-oxopyridine-3-carboxylic acid (2e): Yield 75%, brown solid, mp 156-158 ^{o}C; **^{1}H NMR** (400 MHz, DMSO): δ 3.70 (s, 3H), 6.43 (d, 1H), 6.75 (d, 1H), 7.53 (m, 2H), 8.26 (s, 1H), 9.61-9.64 (m, 1H), 11.0(d, 1H); **^{13}C NMR** (4000 MHz, DMSO): δ 56.0, 103.1, 114.5, 119.4, 122.6, 139.0, 142.2, 161.2, 166.0; IR (KBr) 3260, 3010, 2920, 2860, 17880, 1660, 1590, 1120 cm^{-1}; **MS**: m/z 245.0 (M+).

1,6-dihydro-1-(4-nitrophenyl)-6-oxopyridine-3-carboxylic acid (2f): Yield 78%, brown solid, mp 120-122 ^{o}C; **^{1}H NMR** (400 MHz, DMSO): δ 6.43 (d, 1H), 7.53 (d, 2H), 7.75 (d, 2H), 8.26 (d, 1H), 11.0(d, 1H); **^{13}C NMR** (400 MHz, DMSO): δ 103.5, 119.0, 122.6, 121.6, 139.4, 142.4, 161.2, 166.4; **IR** (KBr) 3260, 3040, 2900, 2840, 1810, 1670, 1580 cm^{-1}; **MS**: m/z 260.04 (M+).

Step II (General synthesis of N-carbamoyl-6-oxo-1-phenyl-1, 6-dihydropyridine-3-carboxy derivatives) A_1-A_6

The methyl 1, 6-dihydro-6-oxopyridine-3-carboxylate derivatives (**2a-f)** was reacted with thionyl chloride in the presence of base and kept on reflux for 5 to 6 hrs. This reaction mixture was further treated with urea which was kept on magnetic stirrer.

N-carbamoyl-6-oxo-1-phenyl-1,6 dihydropyridine-3-carboxamide (A1): The Methyl 1,6-dihydro-6-oxo-1-phenylpyridine-3-carboxylate (2a) was hydrolyzed by adding aqueous acid and heat the mixture and it hydrolyzed carboxylic ester to corresponding acid. Then added thionyl chloride in the presence of base and kept on reflux for 5 to 6 hrs. After completion the reaction urea was dissolved in water and added to above reaction mixtures with constant stirring.

Spectral Analysis:

Molecular Formula $C_{13}H_{11}N_3O_3$**,** Yield 84%, brown solid, mp 168-170 ^{o}C; **Mol. Wt:** 257.08**; IR: 3150**, 1650, 3050, 2140, 1710, 1670, 1620 cm^{-1}; **H^{1} NMR**(400 MHz, DMSO)**: δ**10.20(d, 1H),7.30 & 7.10 (m, 2H), 6.90, 6.50(m, 2H), 6.19(s, 2H); C^{13} NMR: **δ** 160, 154, 140, 128, 118, 114; **Mass: m/e=** 257.08 **Elemental Analysis:** C-60.70, H-4.30, N-16.30, O-18.6.

(ii) Synthesis of A2 compound:

The Methyl 1-(4-chlorophenyl)-1,6-dihydro-6-oxopyridine-3-carboxylate (2b) was hydrolyzed by adding aqueous acid and heat the mixture and it hydrolyzed carboxylic ester to corresponding acid. Then added thionyl chloride in the presence of base and kept on reflux for 5 to 6 hrs. After completion the reaction urea was dissolved in water and added to above reaction mixtures with constant stirring.

Spectral Analysis:

Molecular Formula $C_{13}H_{10}ClN_3O_3$, Mol. Wt.-291.69; **IR:** 3340, 1710, 3160, 2180, 1730, 1690, 1650, 760; **H^{1} NMR:** 6.11(d, 2H), 10.10(s, 1H), 6.42 & 6.80(m, 2H), 7.20 & 7.59(m, 4H), 8.18(s, 1H); **C^{13} NMR:** 166,160,154,138, 130, 118, and 114; **Mass:** m/e-291.69;

Elemental analysis:

C-53.2, H-3.50, Cl-12.1, N-14.4, O-16.5.

(iii) Synthesis of N-carbamoyl-1-(4-ethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (A3):

The Methyl 1-(4-ethylphenyl)-1,6-dihydro-6-oxopyridine-3-carboxylate (2c) was hydrolyzed by adding aqueous acid and heat the mixture and it hydrolyzed carboxylic ester to corresponding acid. Then added thionyl chloride in the presence of base and kept on reflux for 5 to 6 hrs. After completion the reaction

urea was dissolved in water and added to above reaction mixtures with constant stirring.

Spectral Analysis:
Molecular Formula: $C_{15}H_{15}N_3O_3$, Mol. Wt-285.3**; IR:** 3190, 1630, 3220, 2920, 1980, 1760, 1650, 1610; **H^1 NMR:** 5.99(d, 1H), 10.01(s, 1H), 6.80, 6.43(d, 2H), 7.60-7.10(m, 4H), 2.60(m, 1H); **C^{13} NMR:** 166, 160, 154, 140, 138, 130, 124; **Mass:** m/e-285.11; **Elemental analysis:** C-63.15, H-5.10, N-14.7, O-16.2.

(iv) Synthesis of N-carbamoyl-1-(2-chloro-4-methylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (A4):
The Methyl 1-(2-chloro-4-methylphenyl)-1,6-dihydro-6-oxopyridine-3-carboxylate carboxylate (2d) was hydrolyzed by adding aqueous acid and heat the mixture and it hydrolyzed carboxylic ester to corresponding acid. Then added thionyl chloride in the presence of base and kept on reflux for 5 to 6 hrs. After completion the reaction urea was dissolved in water and added to above reaction mixtures with constant stirring.

Spectral analysis:
Molecular formula $C_{14}H_{12}ClN_3O_3$, Mol Wt. 305.72, **IR:** 3410, 1670, 3080, 2890, 2210, 1720, 1640, 1610, 690. **H^1 NMR:** 10.04(s, 1H), 6.00(d, 1H), 6.95(m, 1H), 8.30(s, 1H), 7.50(m, 2H), 7.04(m, 2H), 2.40(s, 3H); **C^{13} NMR:** 165, 153, 160, 141, 137.8, 126.9, 23.8; **Mass:** 305.06.

Elemental analysis: C-55.0, H-3.90, Cl-11.6, N-13.8, O-15.5.

(v) Synthesis of N-carbamoyl-1-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (A5):
The Methyl 1,6-dihydro-1-(4-methoxyphenyl)-6-oxopyridine-3-carboxylate (2e) was hydrolyzed by adding aqueous acid and heat the mixture and it hydrolyzed carboxylic ester to corresponding acid. Then added thionyl chloride in the presence of base and kept on reflux for 5 to 6 hrs. After completion the reaction urea was dissolved in water and added to above reaction mixtures with constant stirring.

Spectral analysis:
Molecular formula $C_{14}H_{13}N_3O_4$, Mol Wt. 287.27, **IR:** 3160, 1660, 3100, 3080, 1640, 1690, 1730, 1160; **H^1 NMR:** 3.70(s, 3H), 6.0(d, 1H), 6.95(m, 1H), 6.50(d, 1H), 7.62(m, 2H), 6.70(m, 2H), 8.2(s, 1H), 10.00(d, 1H),); **C^{13} NMR:** 167, 154, 160, 138, 118, 114, 56; **Mass:** m/e 287.2;

Elemental analysis: C-58.6, H-5.0, N-15, O-22.

(vi) Synthesis of N-carbamoyl-1-(4-nitrophenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (A6):
The Methyl 1,6-dihydro-1-(4-nitrophenyl)-6-oxopyridine-3-carboxylate (2f) was hydrolyzed by adding aqueous acid and heat the mixture and it hydrolyzed carboxylic ester to corresponding acid. Then added thionyl chloride in the presence of base and kept on reflux for 5 to 6 hrs. After completion the reaction urea was dissolved in water and added to above reaction mixtures with constant stirring.

Spectral analysis:
Molecular formula $C_{13}H_{10}N_4O_5$, Mol Wt. 302.27, **IR:** 3110, 1640, 3120, 1650, 1660, 1720, 1540 &1360; **H^1 NMR:** 10.02(d, 1H), 6.04(d, 1H), 6.50(d,1H), 6.80(d, 1H), 7.80(m, 2H), 8.31(m, 2H); **C^{13} NMR:** 166, 160, 154, 144, 139, 121, 118, 114; **Mass:** 302.07**,**

Elemental analysis: C-52, H-3.30, N-19.8, O-26.2.

Docking Methodology:
Docking Server offers a web-based, easy to use interface that handles all aspects of molecular docking from ligand and protein set-up. While its user friendly interface enables docking calculation and results evaluation carried out by researchers coming from all fields of biochemistry, Docking Server also provides full control on the setting of specific parameters of ligand and protein set up and docking calculations for more advanced users [28].

The application can be used for docking and analysis of single ligands as well as for high throughput docking of ligand libraries to target proteins [29].

Docking Server integrates a number of computational chemistry software specifically aimed at correctly calculating parameters needed at different steps of the docking procedure, i.e. accurate ligand geometry optimization, energy minimization, charge calculation, docking calculation and protein-ligand complex representation. Thus, the use of Docking Server allows the user to carry out highly efficient and robust docking calculations by integrating a number of popular software used in in silico chemistry into one comprehensive web service [29, 30].

RESULT AND DISCUSSION:

N-carbamoyl-6-oxo-1-phenyl-1, 6-dihydropyridine-3-carboxy derivatives were synthesized by the reaction with coumellic acid with acetyl chloride in the presence of THF and aniline derivatives which were kept for reflux for 10-12 hrs yield yellow rude product which was recrystalized with ethyl acetate and n-hexane(1:2) ratio, give crystalline product of 2-pyridone derivatives (2a-e). Further it were hydrolyzed on heating with aqueous

acid and kept for reflux with Thionyl chloride, which were further treated with urea yield N-carbamoyl-6-oxo-1-phenyl-1, 6-dihydropyridine-3-carboxy derivatives (A1-A6). These derivatives were confirmed by spectral characterization such as IR, H^1 NMR, C^{13} NMR and Mass.

These synthesized compound were docked with FGF1 protein (PDB ID 3K1X), showing good binding affinity with active pocket and all these derivatives (A1-A6) showed more interaction with ligand. This protein functions as a modifier of endothelial cell migration and proliferation, as well as an angiogenic factor. It acts as a mitogen for a variety of mesoderm- and neuroectoderm-derived cells in vitro, thus is thought to be involved in organogenesis. Among the all designed and synthesized 2-pyridone derivatives showed good binding affinity while A4 showing highest binding affinity toward fibroblast growth factor 1 followed by A6, A3, A5, A1 and A2. All the interaction was shown in Figure 4 followed by Figure 6, Figure 3, Figure 5, Figure 1, and Figure 2 respectively, which was depicted in table 1. On the basis of interaction, the compound A4 showed maximum no. of interaction which was written in table 2. After analyzing the result, the synthesized derivatives indicating the good interaction with FGF1 protein, by this inhibit the cell growth. , the inhibitory activity of the target compounds against fibroblast growth factor 1 receptor was evaluated. Results indicated the ability of the target compounds to inhibit FGFR-TK with maximal binding energy in the range of -5.33 to 4.84 kcal/mole (shown in table 1), Which will help to inhibit the outgrowth of cell and can be act as anti cancer agents.

Binding Energy interaction table:

Table 1: Binding energy interaction table with synthesized compound (A1-A6)

Compound	Est. Free Energy of Binding	Est. Inhibition Constant	vdW+Hbond+desolv Energy	Electrostatic Energy	Total Inter molec. Energy	Frequency	Interact. Surface
A1	-4.88 kcal/mol	265.06 uM	-5.41 kcal/mol	-0.15 kcal/mol	-5.55 kcal/mol	100%	546.001
A2	-4.84 kcal/mol	284.16 uM	-5.25 kcal/mol	-0.90 kcal/mol	-6.15 kcal/mol	50%	611.062
A3	-5.15 kcal/mol	168.70 uM	-6.08 kcal/mol	-0.13 kcal/mol	-6.21 kcal/mol	50%	606.773
A4	-5.33 kcal/mol	124.93 uM	-5.94 kcal/mol	-0.08 kcal/mol	-6.02 kcal/mol	100%	588.548
A5	-5.01 kcal/mol	211.36 uM	-5.53 kcal/mol	-0.41 kcal/mol	-5.94 kcal/mol	100%	571.036
A6	-5.20 kcal/mol	154.28 uM	-5.82 kcal/mol	-0.32 kcal/mol	-6.14 kcal/mol	100%	554.599

Interaction table of synthesized compound (A1-A6) with all amino acids:

Table 2: Total no. of Interaction with synthesized compound (A1-A6)

S. No.	Compounds name	No. of Interaction	Detail of interactions			
			Hydrogen Bonds	Polar Bond	Hydrophobic bond	Others
1	A1	28	-	1	2	20
2	A2	15	1	7	2	5
3	A3	40	2	3	5	30
4	A4	28	1	2	-	24
5	A5	31	1	3	1	26
6	A6	27	1	3	1	22

Compound A1: Interaction with ligands

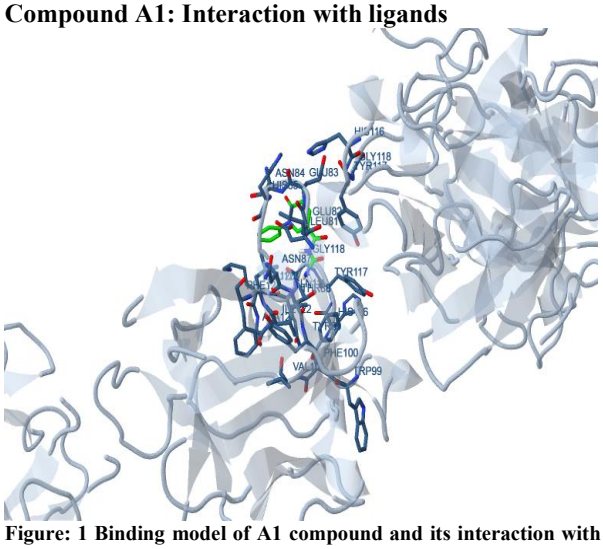


Figure: 1 Binding model of A1 compound and its interaction with FGF1 Receptor (PDB-ID: 3k1X) binding pocket

Compound A2: Interaction with ligands

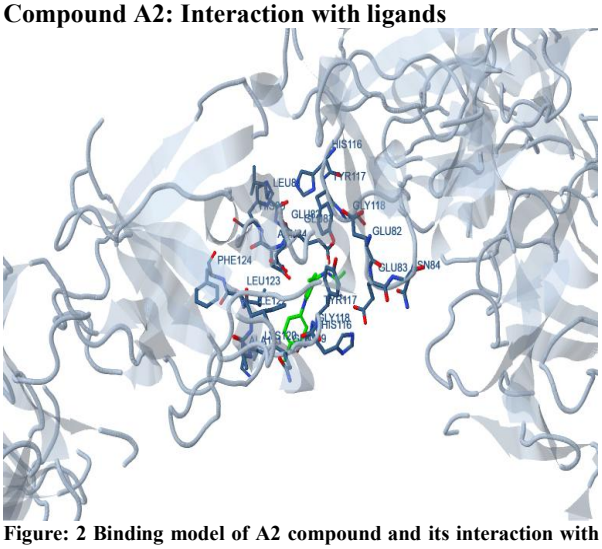


Figure: 2 Binding model of A2 compound and its interaction with FGF1 Receptor (PDB-ID: 3k1X) binding pocket

Compound A3: Interaction with ligands

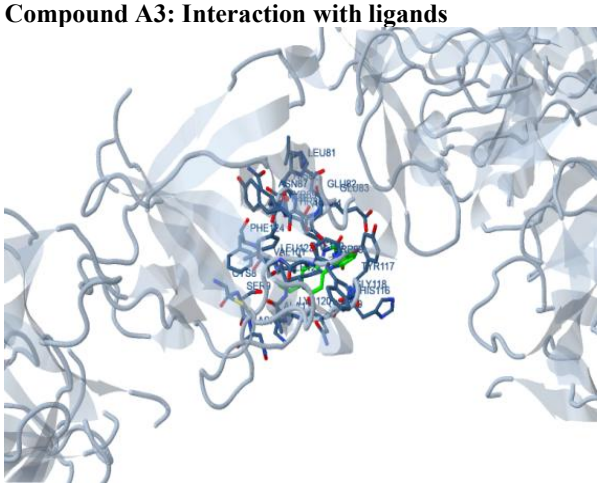


Figure: 3 Binding model of A3 compound and its interaction with FGF1 Receptor (PDB-ID: 3k1X) binding pocket

Compound A4: Interaction with ligands

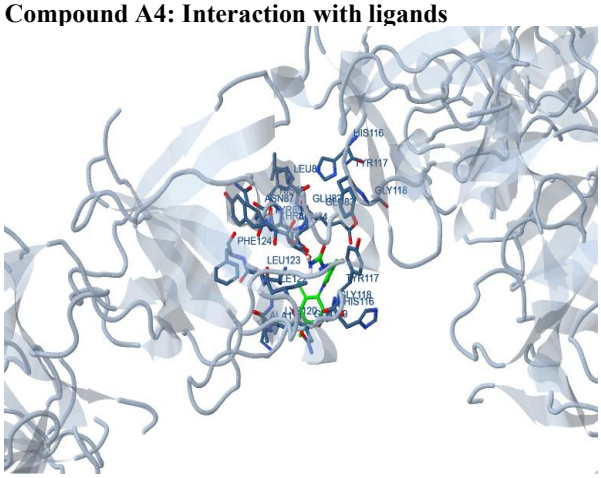


Figure: 4 Binding model of A4 compound and its interaction with FGF1 Receptor (PDB-ID: 3k1X) binding pocket

Compound A5: Interaction with ligands

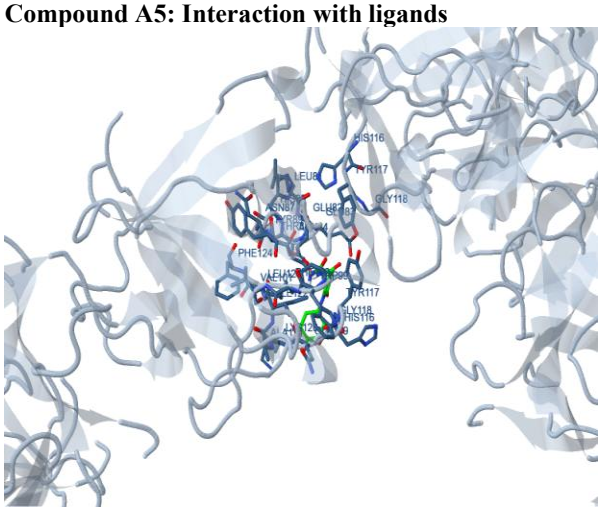


Figure: 5 Binding model of A5 compound and its interaction with FGF1 Receptor (PDB-ID: 3k1X) binding pocket

Compound A6: Interaction with ligands

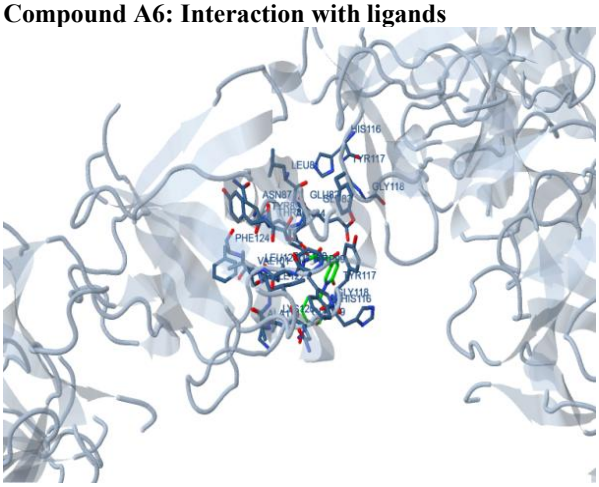


Figure: 6 Binding model of A6 compound and its interaction with FGF1 Receptor (PDB-ID: 3k1X) binding pocket

CONCLUSION:

The N-carbamoyl-6-oxo-1-phenyl-1, 6-dihydropyridine-3-carboxamide motif was design, synthesized and identified by screening as a promising lead scaffold for anti-cancer activity against fibroblast growth factor 1. This work describes the synthesis of a N-carbamoyl-6-oxo-1-phenyl-1, 6-dihydropyridine-3-carboxamide as well as five derivatives containing different substitution on N-phenyl ring. The methodology involved the reaction between molecule 1 with acetyl chloride, followed by aniline derivatives. The reaction mixture (2a-f) was treated with under specific conditions yield compound A1-A6. Structures of the newly synthesized compounds were proven by spectral method. The two most potent analogues A4 and A6 showed lowest estimated molecular binding energy against fibroblast growth factor 1. Furthermore, these two compounds displayed selectivity for ovarian cancer cell over normal human fibroblast growth factor.

ACKNOWLEDGEMENT:

The authors are thankful to Vels University (VISTAS) and its management for providing research facilities and encouragement.

REFERENCES:

1. Dusan Z. Mijin, Jelena M. Markovic, Danijela V. Brkovic, Aleksandar D. Marinkovic, Microwave-assisted synthesis of 2-pyridone and 2-pyridone-based Compounds; Hem. Ind. 68 (1) (2014) 1–14.
2. Chand, K., Prasad, S., Tiwari, R. K., Shirazi, A. N., Kumar, S., Parang, K., & Sharma, S. K, Synthesis and evaluation of c-Src kinase inhibitory activity of pyridin-2(1H)-one derivatives. Bioorganic Chemistry. 2014, 2-23.
3. Mohammad Seifi, Mahboobeh Khajehasani Rabori, Hassan Sheibani; Highly Efficient Method for Synthesis of N-Amino-2-Pyridone Derivatives in the Presence of Catalysts such as Magnesium Oxide (MgO) and Bismuth(III) Nitrate Pentahydrate ($Bi(NO3)_3 \cdot 5H_2O$); Modern Research in Catalysis, 2, 2013 8-12.

4. Henning Jacob Jessen and Karl Gademann; 4-Hydroxy-2-pyridone alkaloids: Structures and synthetic approaches Nat. Prod. Rep., 27; 2010; 1168–1185.
5. E. Dilip de Silva, Anna-Skrollan Geiermann, Maya I. Mitova, Philipp Kuegler, John W. Blunt, Anthony L. J. Cole and Murray H. G. Munro; Isolation of 2-Pyridone Alkaloids from a New Zealand Marine-Derived *Penicillium* species. J. Nat. Prod., 72; 2009; 477–479.
6. Christian B. Fischer, Kurt Polborn, Harald Steininger, and Hendrik Zipse, Synthesis and solid-state structures of alkyl-substituted 3-cyano-2-pyridones; Z. Naturforsch. 59b; 2004; 1121-1131.
7. Bernard Thisse, Christine Thisse, "Functions and regulations of fibroblast growth factor signaling during embryonic development", Developmental Biology 287; 2005; 390 – 402.
8. Amaya, E., Musci, T.J., Kirschner, M.W,. Expression of a dominant negative mutant of the FGF receptor disrupts mesoderm formation in Xenopus embryos. Cell 66 (2), 1991; 257– 270.
9. Barnett, M.W., Old, R.W., Jones, E.A., 1998. Neural induction and patterning by fibroblast growth factor, notochord and somite tissue in Xenopus. Dev. Growth Differ. 40 (1), 47–57.
10. Eswarakumar V.P., Lax I., Schlessinger J. Cellular signaling by fibroblast growth factor receptors; Cytokine & Growth Factor Reviews; 16; 2005; 139–149.
11. Gospodarowicz D. Localisation of a fibroblast growth factor and its effect alone and with hydrocortisone on 3T3 cell growth. Nature 249; 1974; 123–7.
12. Ornitz DM, Itoh N. Fibroblast growth factors. Genome Biol, 2; 2001; 3005 [Reviews].
13. Givol D, Eswarakumar VP, Lonai P. Molecular and cellular biology of FGF signaling. In: Epstein CJ, Erickson RP, Wynshaw-Boris A, editors. Inborn errors of development – the molecular basis of clinical disorders of morphogenesis. Oxford: Oxford University Press; 2003; 367–79.
14. Mohammadi M, Schlessinger J, Hubbard SR. Structure of the FGF receptor tyrosine kinase domain reveals a novel autoinhibitory mechanism. Cell; 86; 1996; 577–87.
15. Mohammadi M, McMahon G, Sun L, Tang C, Hirth P, Yeh BK, et al. Structures of the tyrosine kinase domain of fibroblast growth factor receptor in complex with inhibitors. Science 276; 1997; 955–60.
16. Fioretos T, Panagopoulos I, Lassen C, Swedin A, Billstrom R, Isaksson M, et al. Fusion of the BCR and the fibroblast growth factor receptor-1 (FGFR1) genes as a result of t(8;22)(p11;q11) in a myeloproliferative disorder: the first fusion gene involving BCR but not ABL. Genes Chromosomes Cancer ; 32;2001; 302–10.
17. Antonio Jacinto Demuner , Vania Maria Moreira Valente , Luiz Cláudio Almeida Barbosa , Akshat H. Rathi , Timothy J. Donohoe and Amber L. Thompson, Synthesis and Phytotoxic activity of new Pyridones derived from 4-Hydroxy-6-Methylpyridin-2(1H)-one" Molecules, 14, 2009, 4973-4986.
18. Ebtehal S. Al-Abdullah synthesized "Synthesis and anticancer activity of some noveltetralin-6-yl-pyrazoline, 2-thioxopyrimidine, 2-oxopyridine,2-thioxo-pyridine and 2-iminopyridine derivatives" Molecules, *16*; 2011; 3410-3419.
19. Zhiliang Lv, Chunquan Sheng, Tiantian Wang, Yikai Zhang, Jia Liu, Jilu Feng, Hailing Sun, Hanyu Zhong, Chunjuan Niu, and Ke Li; Design, Synthesis, and Antihepatitis B Virus Activities of Novel 2-Pyridone Derivatives; J. Med. Chem. 53; 2010; 660–668.
20. Lisa Dailey, Davide Ambrosetti, Alka Mansukhani, Claudio Basilico, Mechanisms underlying differential responses to FGF signaling; Cytokine & Growth Factor Reviews 16; 2005; 233–247.
21. Arora Amit and Eric M, Role of Tyrosine Kinase Inhibitors in Cancer Therapy; Journal of Pharmacology and Experimental Therapeutics; 315 (3) 2005; 971-979.
22. "Ovarian Cancer Prevention (PDQ®)". NCI. 2013.
23. Ovarian cancer risks and causes". Cancer Research UK. 15 January 2014. Retrieved 29 January 2015
24. Hartmann JT, Haap M, Kopp HG, Lipp HP, "Tyrosine kinase inhibitors - a review on pharmacology, metabolism and side effects", Curr Drug Metab. 10(5); 470-81.
25. Faivre S, Djelloul S, Raymond E, New paradigms in anticancer therapy: targeting multiple signaling pathways with kinase inhibitors. Semin Oncol. 33(4) 2006; 407-20.
26. Young Kwan Ko, Seung Chul Lee, Dong Wan Koo, Mankil Jung, and Dae-Whang Kim, A new and Facile Synthesis of 2-Pyridones, *Bull. Korean Chem. Soc*. 2001, Vol. 22, No. 2.
27. Chaudhary Rakhi, Shuaib, S. Riaz Hashim and Mishra P. S., "Synthesis, characterization and tubulin-interaction profile of substituted Cinnamoyl urea derivatives" Der Pharma Chemica, 7(10); 2015; 493-503.
28. Chaudhary Rakhi, Shuaib, S. Riaz Hashim and Mishra P. S., Synthesis, Characterization and Antitumor potential of Cinnamoyl urea derivatives; Asian Journal of Chemistry, 28(2); 2016, 410-415.