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RESEARCH ARTICLE

Design, Synthesis and Characterization of 2-pyridone Derivatives as C-Jun N-terminal Kinases (JNKs) Signaling Pathway Inhibitors

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ABSTRACT:
A new series of 2-pyridone derivatives (A1-A6) were synthesized by various substitution and their structures were confirmed by spectral and elemental analyses. The cytotoxic activities of the newly synthesized compounds were docked against JNKs (2WAJ Transferase). JNKs pathway regulates various physiological processes including inflammatory responses, cell differentiation, cell proliferation, cell death, cell survival and expression of proteins. The molecular docking study was used for confirming their interaction with c-Jun N-terminal kinases (JNKs). Through *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 were considered as good JNKs inhibitors. This will help to inhibit the outgrowth of cell and can be act as good anti cancer agents.

KEYWORDS: 2-pyridone derivatives, JNKs signaling, 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 [1]. 2-Pyridone derivatives are especially interesting because the 2-pyridone structure is present in many compounds of natural origin. Due to a variety of pharmacological properties, the 2-pyridone structure is important in the pharmaceutical industry [2].

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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:
It is an abnormal growth of cells which tend to proliferate in an uncontrolled way and in some cases, to metastasize (spread). Cancer can involve any tissue of the body and have many different forms in each body area. Most cancers are named for the type of cell or organ in which they start. If a cancer spreads (metastasizes), the new tumor bears the same name as the original (primary) tumor [5]. The frequency of a particular cancer may depend on gender. While skin cancer is the most common type of malignancy for both men and women, the second most common type in men is prostate cancer and in women, breast cancer. C-jun is a proto-oncogene (its protein is Jun) and is the cellular homolog of the viral oncoprotein v-jun. Jun is the first

discovered oncogenic transcription factor. A study with a group consisted of 103 cases of phase I/II invasive breast cancers showed that activated c-jun is expressed predominantly at the invasive front of breast cancer and is associated with proliferation and angiogenesis [6].

Cell Cycle Progression:
Studies show that c-jun is required for progression through the G1 phase of the cell cycle, and c-jun null cells show increased G1 arrest [7]. C-jun regulates the transcriptional level of cyclin D1, which is a major Rb kinase. Rb is a growth suppressor, and it is inactivated by phosphorylation. Therefore, c-jun is required for maintaining sufficient cyclin D1 kinase activity and allowing cell cycle progression [8].

Breast Cancer:
Over expression of c-jun in MCF-7 cells can result in overall increased aggressiveness, as shown by increased cellular motility, increased expression of a matrix-degrading enzyme MMP-9, increased *in-vitro* chemoinvasion and tumor formation in nude mice in the absence of exogenous estrogens [9]. The MCF-7 cells with c-jun over expression became unresponsive to estrogen and tamoxifen, thus c-jun over expression is proposed to lead to an estrogen-independent phenotype in breast cancer cells. The observed phenotype for MCF-7 cells with c-jun over expression is similar to that observed clinically in advanced breast cancer, which had become hormone unresponsive this study showed increased *in-vivo* liver metastasis by the breast cancer with c-jun over expression. This finding suggests that c-jun plays a critical role in the metastasis of breast cancer[9, 10].

As Anti-Cancer Drug Target:
A study showed that oncogenic transformation by ras and fos requires Jun N-terminal phosphorylation at Serine 63 and 73 by the Jun N- terminal kinases (JNK). Therefore, targeting the N-terminal phosphorylation of Jun (or the JNK signaling pathway) can be a potential strategy for inhibiting tumor growth [11].

C-Jun N-terminal kinases (JNKs), were originally identified as kinases that bind and phosphorylate c-Jun on Ser-63 and Ser-73 within its transcriptional activation domain. They belong to the mitogen-activated protein kinase family and are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock [12]. They also play a role in T cell differentiation and the cellular apoptosis pathway. Activation occurs through a dual phosphorylation of threonine (Thr) and tyrosine (Tyr) residues within a Thr-Pro-Tyr motif located in kinase subdomain VIII [13]. Activation is carried out by two MAP kinases, MKK4 and MKK7 and JNK can be inactivated by Ser/Thr and Tyr protein phosphatases [14]. The c-Jun N-terminal kinases consist of ten isoforms derived from three genes: JNK1 (four isoforms), JNK2 (four isoforms) and JNK3 (two isoforms) [15]. Each gene is expressed as either 46 kDa or 55 kDa protein kinases, depending upon how the 3' coding region of the corresponding mRNA is processed, however, a second form of alternative splicing occurs within transcripts of JNK1 and JNK2, yielding JNK1-α, JNK2-α and JNK1-β and JNK2-β. Differences in interactions with protein substrates arise because of the mutually exclusive utilization of two exons within the kinase domain [16]. c-Jun N-terminal kinase isoforms have the following tissue distribution:

- JNK1 and JNK2 are found in all cells and tissues.
- JNK3 is found mainly in the brain, but is also found in the heart and the testes.

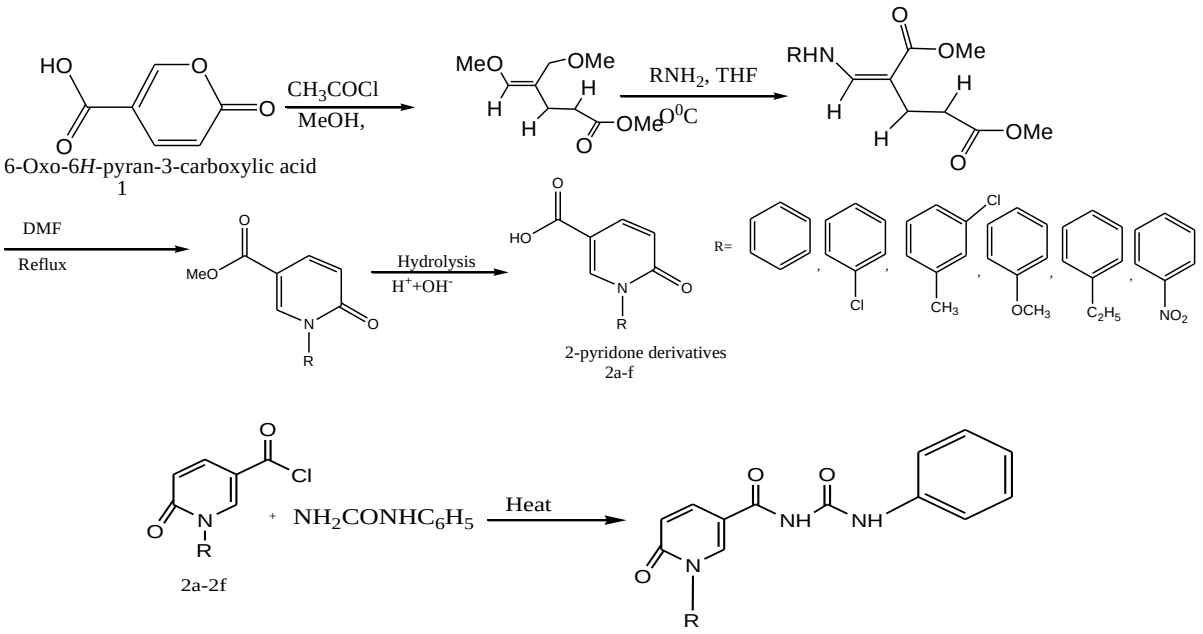
Inhibitors of c-jun-N-Terminal Kinase (JNK) have many potential therapeutic indications ranging from cancer, neurodegenerative disease, metabolic disorders, inflammation and cardiovascular disease [17]. This overview will highlight biological inhibitors such as JNK-interacting protein (JIP) as well as small molecule inhibitors from various structural classes including, aminopyrimidines and indazoles [18].

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 ($\delta = 0$). 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.

Scheme:

STEP -I



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 0ºC. 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 hydrolyzed 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 [19].

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 156-158ºC; **^{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 ºC; **^{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 ºC; **^{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:

(I) **1-(6-Oxo-1-phenyl-1,6-dihydro-pyridine-3-carbonyl)-3-phenyl-urea** (**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 3 to 4 hrs. After completion the reaction phenyl urea was dissolved in water and added to above reaction mixtures with constant stirring.

Spectral Analysis:

Molecular formula: $C_{19}H_{15}N_3O_3$; Mol. Wt: 333.29; **IR:** 3059(Ar-H), 783(Ar-H), 1650 (C=C of Ar), 3393(N-H) 1682(C=O), 1691(C=O), 1649 (N-R_3), **H^{1} NMR:** 6.01(d, 1H), 6.40(d, 1H), 6.95(m, 1H), 7.24(m, 2H), 7.64(m, 2H), 8.23(s, 1H), 10.0(d, 1H). **C^{13} NMR:** 114.5, 19.1, 121.5, 124.2, 129.1, 135.4, 138.2, 139.2, 149.1, 160.6, 166.2.; **Mass:** m/e 333.11, **Elemental analysis:** C 68.4, H 4.54, N 12.6, O 14.4.

(II) **1-[1-(4-Chloro-phenyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyl]-3-phenyl-urea** (**A2):** 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 3 to 4 hrs. After completion the reaction phenyl urea was dissolved in water and added to above reaction mixtures with constant stirring.

Spectral Analysis:

Molecular formula: $C_{19}H_{14}ClN_3O_3$; Mol. Wt: 367.79; **IR:** 3056(Ar-H), 781(Ar-H), 1662 (C=C of Ar), 3390(N-H) 1684(C=O), 1692(C=O), 1646 (N-R_3), 680 (C-Cl); **H^{1} NMR:** 6.0(d, 1H), 6.42(d, 1H), 6.95(m, 1H), 7.24(m, 2H), 7.64(m, 2H), 8.20(s, 1H), 10.0(d, 1H). **C^{13} NMR:** 114.5, 19.1, 121.5, 124.2, 129.1, 135.4, 138.2, 139.2, 149.1, 160.6, 166.2.; **Mass:** m/e 367.7, **Elemental analysis:** C 62.05, H 3.80, Cl 9.50, N 11.6, O 13.7.

(III) **Synthesis of 1-[1-(4-Ethyl-phenyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyl]-3-phenyl-urea (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 phenyl urea was dissolved in water and added to above reaction mixtures with constant stirring.

Spectral Analysis:

Molecular formula $C_{21}H_{19}N_3O_3$, Mol. Wt 361.69, **IR:** 3062(Ar- H), 780(Ar-H), 1654 (C=C of Ar), 3396(N-H) 1680(C=O), 1695(C=O), 1655 (N-R_3), 2942, 1456, 1373(CH_3, CH_2); **H^{1} NMR:** 1.24(m, 3H), 2.60(m, 2H), 6.0(d, 1H), 6.43(d, 1H), 6.95(m, 1H), 7.10(m, 2H), 7.24(m, 2H), 7.64(m, 2H), 8.21(s, 1H), 10.0(d, 1H); C^{13} NMR: 14.6, 32.5, 114.5, 119.0, 121.6, 124.2, 129.2, 135.4, 139.2, 148.8, 160.4, 166.3; Mass: m/e 361.14; Elemental analysis: C 69.8, H 5.40, N 11.6, O 13.3.

(IV) **1-[1-(2-Chloro-4-methyl-phenyl)-6-oxo-1,6-dihydro-pyridine-3-carbonyl]-3-phenyl-urea (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:

$C_{20}H_{16}ClN_3O_3$, Mol. Wt 381.81, **IR:** 3062(Ar-H), 780(Ar-H), 1654 (C=C of Ar), 3396(N-H) 1680(C=O), 1695(C=O), 1655 (N-R_3), 2942, 1456, 1373(CH_3, CH_2); **H^{1} NMR:** 2.35(s, 3H), 6.0(d, 1H), 6.43(d, 1H), 6.95(m, 1H),6.92 (m, 1H), 7.24(m, 2H), 7.45(m, 1H), 7.64(m, 1H), 8.20(s, 1H), 10.0(d, 1H), **C^{13} NMR:** 23.8, 114.2, 119.0, 121.9, 122.8, 124.5, 127.0, 130.1, 132.7, 135.9, 138.2,149.1, 160.9, 166.2; **Mass:** m/e 381.09.

(V) **1-(4-methoxyphenyl)-6-oxo-*N*-(phenylcarbamoyl)-1,6-dihydropyridine-3-carboxamide (A5):** 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 3 to 4 hrs. After completion the reaction phenyl urea was dissolved in water and added to above reaction mixtures with constant stirring.

Spectral analysis: Molecular formula

$C_{20}H_{17}N_3O_4$, Mol. Wt. 363.37, **IR:** 065(Ar-H), 784(Ar-H), 1658 (C=C of Ar), 3398(N-H) 1686(C=O), 1698(C=O), 1658 (N-R_3), 1234, 1008(C-O); **H^{1} NMR**: 3.75(d, 1H), 6.0(d, 1H), 6.44(d, 1H), 6.75(m, 2H), 6.95(d, 1H), 7.00(m, 1H), 7.24(m, 2H), 7.53(m, 2H),

7.63(m, 2H), 8.20(d, 1H), 10.1(d, 1H); **C^{13} NMR: 56.0,** 115.2, 119.1, 121.5, 122.6, 124.8, 129.1, 135.2, 138.4, 139.3, 149.1, 156.2, 160.8, 166.2; **Mass:** m/e 363.12; **Elemental analysis:** C 66.1, H 4.80, N 11.5, O 17.6;

(VI) **Synthesis of 1-(4-nitrophenyl)-6-oxo-*N*-(phenylcarbamoyl)-1,6-dihydropyridine-3-carboxamide (A6):**

(VII) 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 3 to 4 hrs. After completion the reaction phenyl urea was dissolved in hot water and added to above reaction mixtures with constant stirring.

Spectral Analysis:

Molecular formula $C_{19}H_{14}N_4O_5$, Mol. Wt. 378.34, **IR:** 3056 (Ar-H), 787(Ar-H), 1656 (C=C of Ar), 3390(N-H), 1686(C=O), 1696(C=O), 1653 (N-R_3), 1343(C-N), 1524(N=O), **H^1 NMR:** 6.0(d, 1H), 6.43(d, 1H), 7.0(m, 1H), 7.24(m, 2H), 7.64(m, 2H),7.90(m, 2H), 8.179m, 2H), 10.0(d, 1H); **C^{13} NMR:** 114.5, 118.3, 121.5, 124.3, 129.0, 135.9, 139.5, 144.3, 148.2, 161.2, 166.5; **Mass:** m/e 378.10, **Elemental analysis:** C 60.3, H 3.7, N 14.8, O 21.14.

Docking Methodology:

Docking Server offers a web-based, assay 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 [19].

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 [20]. 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 [21].

RESULT AND DISCUSSION:

2-pyridone derivatives were synthesized by the reaction of coumellic acid with acetyl chloride in the presence of THF. The reaction mixture was treated with aniline derivatives, which were kept on reflux for 10-12 hrs, yield yellow crude 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 phenyl 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 spectroscopy.

These synthesized compound were docked with JNKs protein (PDB ID: 2WAJ transferase), showing good binding affinity with active pocket and all these derivatives (A1-A6) showed good 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 neuro-ectoderm 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 A1 showing highest binding affinity among all synthesized compounds toward JNKs followed by A6, A5, A4, A3 and A2 and all the interaction were shown in Figure 1 followed by Figure 6, Figure 5, Figure 4, Figure 3, and Figure 2 respectively, Which was depicted in table 1. After analyzing the result, the synthesized derivatives indicating the good interaction with c-Jun N-terminal Kinases (WAJ Transferase), by this, inhibit the cell growth. The inhibitory activity of the targeted protein JNKs against synthesized compounds (ligands) were evaluated. The results indicated the ability of the target compounds to inhibit cJNKs with maximal binding energy in the range of -7.77 to -7.27 kcal/mole shown in table 1. This will help to inhibit the outgrowth of cell and can be act as good 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	-7.77 kcal/mol	2.02 uM	-9.08 kcal/mol	+0.08 kcal/mol	-9.00 kcal/mol	100%	885.748
A2	-7.27 kcal/mol	4.69 uM	-8.23 kcal/mol	+0.05 kcal/mol	-8.18 kcal/mol	50%	808.132
A3	-7.31 kcal/mol	4.38 uM	-8.58 kcal/mol	-0.02 kcal/mol	-8.59 kcal/mol	50%	881.069
A4	-7.36 kcal/mol	4.04 uM	-8.63 kcal/mol	+0.04 kcal/mol	-8.58 kcal/mol	50%	908.12
A5	-7.42 kcal/mol	3.67 uM	-8.62 kcal/mol	-0.05 kcal/mol	-8.67 kcal/mol	50%	937.442
A6	-7.57 kcal/mol	2.83 uM	-8.80 kcal/mol	-0.02 kcal/mol	-8.82 kcal/mol	50%	869.705

Compound: A1

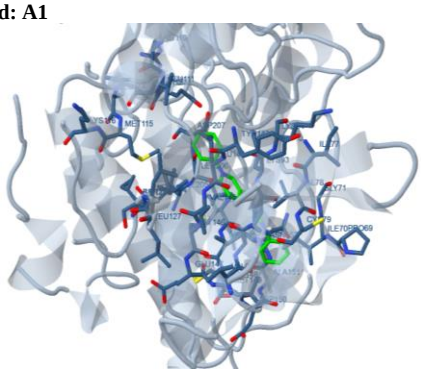


Figure 1: Binding model of A1 compound and its interaction with c-Jun N-terminal Kinases (JNKs) Signaling Pathway inhibitors (PDB-ID: 2WAJ Transferase) binding pocket

Compound A2.

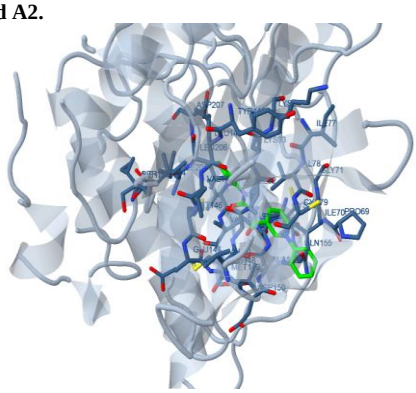


Figure 2: Binding model of A2 compound and its interaction with c-Jun N-terminal Kinases (JNKs) Signaling Pathway inhibitors (PDB-ID: 2WAJ Transferase) binding pocket.

Compound A3

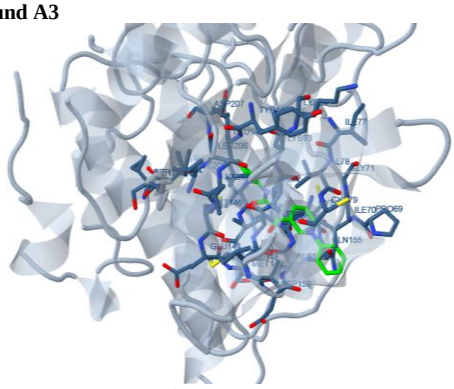


Figure 3: Binding model of A3 compound and its interaction with c-Jun N-terminal Kinases (JNKs) Signaling Pathway inhibitors (PDB-ID: 2WAJ Transferase) binding pocket

Compound A4

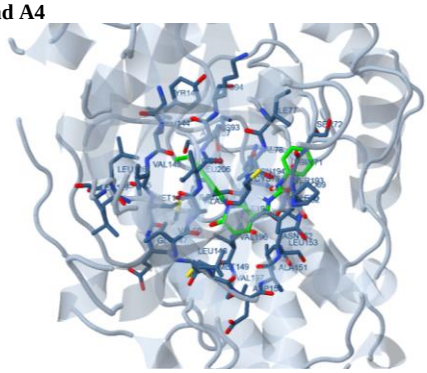


Figure 4: Binding model of A4 compound and its interaction with c-Jun N-terminal Kinases (JNKs) Signaling Pathway inhibitors (PDB-ID: 2WAJ Transferase) binding pocket

Compound A5

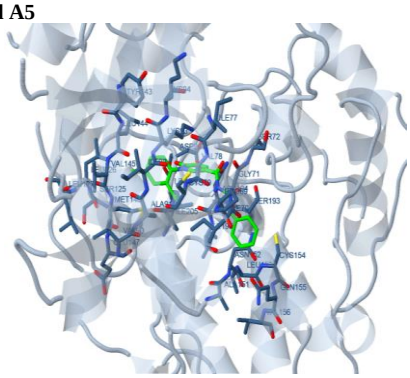


Figure 5: Binding model of A5 compound and its interaction with c-Jun N-terminal Kinases (JNKs) Signaling Pathway inhibitors (PDB-ID: 2WAJ Transferase) binding pocket

Compound A6

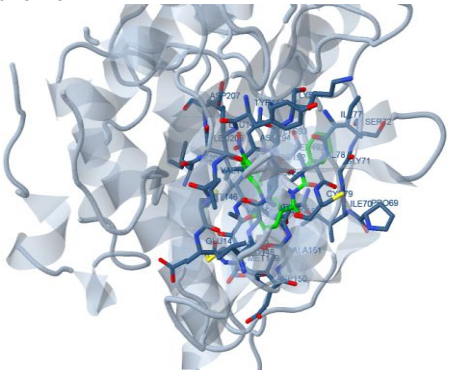


Figure 6: Binding model of A6 compound and its interaction with c-Jun N-terminal Kinases (JNKs) Signaling Pathway inhibitors (PDB-ID: 2WAJ Transferase) binding pocket

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 JNKs inhibitor pathway. This work describes the synthesis of an 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 molecules 1 with acetyl chloride, followed by aniline derivatives. The reaction mixture (2a-f) was treated under specific conditions yield compound A1-A6. Structures of the newly synthesized compounds were proven by spectral method. The most potent analogues A1 and A6 showed highest estimated molecular binding energy against c-Jun N-terminal Kinases (WAJ Transferase), Furthermore, these compounds displayed selectivity for breast cancer cell over normal human c-Jun N-terminal Kinases (WAJ Transferase), signaling pathway inhibitors.

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