

## Synthesis and Biological Evaluation of 2-Substituted-Aryl- 3-Substituted- Phenyl- Oxazole- 4-Thiazolidines as Cyline-Dependent Protein Kinase 2 (CDK2) Inhibitors

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### Abstract

A series of diverse heterocycles of 2-amino-4-phenyl thiazole (1a-o), 2-imine substituted phenyl-4-phenyl thiazole (2a-o) and 2- substituted- aryl- 3- substituted- phenyl- oxazole- 4-thiazolidines (3a-o) were prepared with excellent yield. The synthesized compounds were characterized by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR & Mass spectral analysis. Induced-fit molecular docking (IFD) was performed on analogues of 2-Substituted-Aryl- 3-Substituted- Phenyl- Oxazole- 4- Thiazolidines against target protein (PDB ID 3EZR) having natural kinase inhibitor 3-methoxy-4-{3-[4-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-indazol-6-yl} aniline and synthesized derivatives were carried out against CDK2 using Auto dock tools. Further in vitro studies were evaluated for their antimicrobial and antifungal activities. These heterocycles have been tested against Gram-positive and Gram-negative bacteria and fungi and show outstanding therapeutic activity.

**Keywords:** 2- substituted - aryl- 3- substituted phenyl- oxazole- 4-thiazolidines; 2-imine; 4 phenyl thiazole; molecular docking; CDK inhibitors; Induced-fit molecular docking

## Introduction

In the history of life, heterocyclic compounds have been utilised as colours, pharmaceuticals, and in many commercially important species and their analogues in which one or more ring carbons have been replaced by a heteroatom, such as nitrogen, oxygen, sulphur, phosphorus, silicon, or a metal, among other things. Nitrogen, oxygen, or both are present in the most prevalent heterocyclic systems. The most common and popular methods for preparing heterocyclic compounds is cyclization of suitable compounds. 4-Thiazolidinones are derivatives or Thiazolidine with a carbonyl group at the 4-position substitution is possible at 2, 3 and 5-position [1-2]. The nucleus is also known as the “wonder nucleus” since it produces a variety of derivatives with various biological activity. As a result, thiazolidinone with various substituents has been produced and used as a better medicinal agent in recent years. 4-oxo-thiazolidines are the most widely studied class of chemicals, with antibacterial, anti-inflammatory, anti-HIV, antitubercular, antioxidant, and analgesic properties [3-8]. The nucleus of 4-thiazolidinones has a distinctive role in medicinal actions such as antibacterial, anticancer, antiviral, cardiovascular, antitumor, and CNS depressive.

## Experimental

The melting points were measured in uncorrected open capillary tubes. A Perkin-Elmer 157 spectrometer was used to measure IR spectra in KBr pellets. TMS was used as an internal standard in the recording of H1 NMR spectra in a CDCL<sub>3</sub> on a Bruker- variaiah 300MHz FT NMR spectrometer. TLC on silica gel G plates was used to evaluate the purity of the compounds, and exposure to iodine vapours was used to find the spots.

## Method of Synthesis

### Synthesis of 2-amino, 4-substituted phenyl thiazole

In 100ml of ethanol, substituted acetophenone (0.1mole) and thiourea (0.2mole) were refluxed overnight with Br<sub>2</sub> -H<sub>2</sub>O. Other chemicals were also crystallised from DMF to produce a solid substance.

### Synthesis of 2-imine substituted phenyl 4-substituted phenyl thiazole

A mixture of compound I (0.01mole) and substituted benzaldehyde (0.01mole) on discovery in ethanol in presence of Glacial acetic acid. The reaction mixture was refluxed for 12-

14hr and resulting solid was washed with ether and crystallized from DMF similarly other compound were also prepared.

### Synthesis of 2-[4 oxo-2-substituted-aryl Thiazolidinyl] substituted phenyl thiazole:

In dry benzene, a mixture of compound 2 (0.01mole) and anhydrous ZnCl<sub>2</sub> (one pinch) was added drop by drop with stirring, and the mixture was held at room temperature for 3 days before being refluxed for 12 hours. The resultant solid was washed and recrystallized from DMF after the react mixture was filtered and placed on to ice.

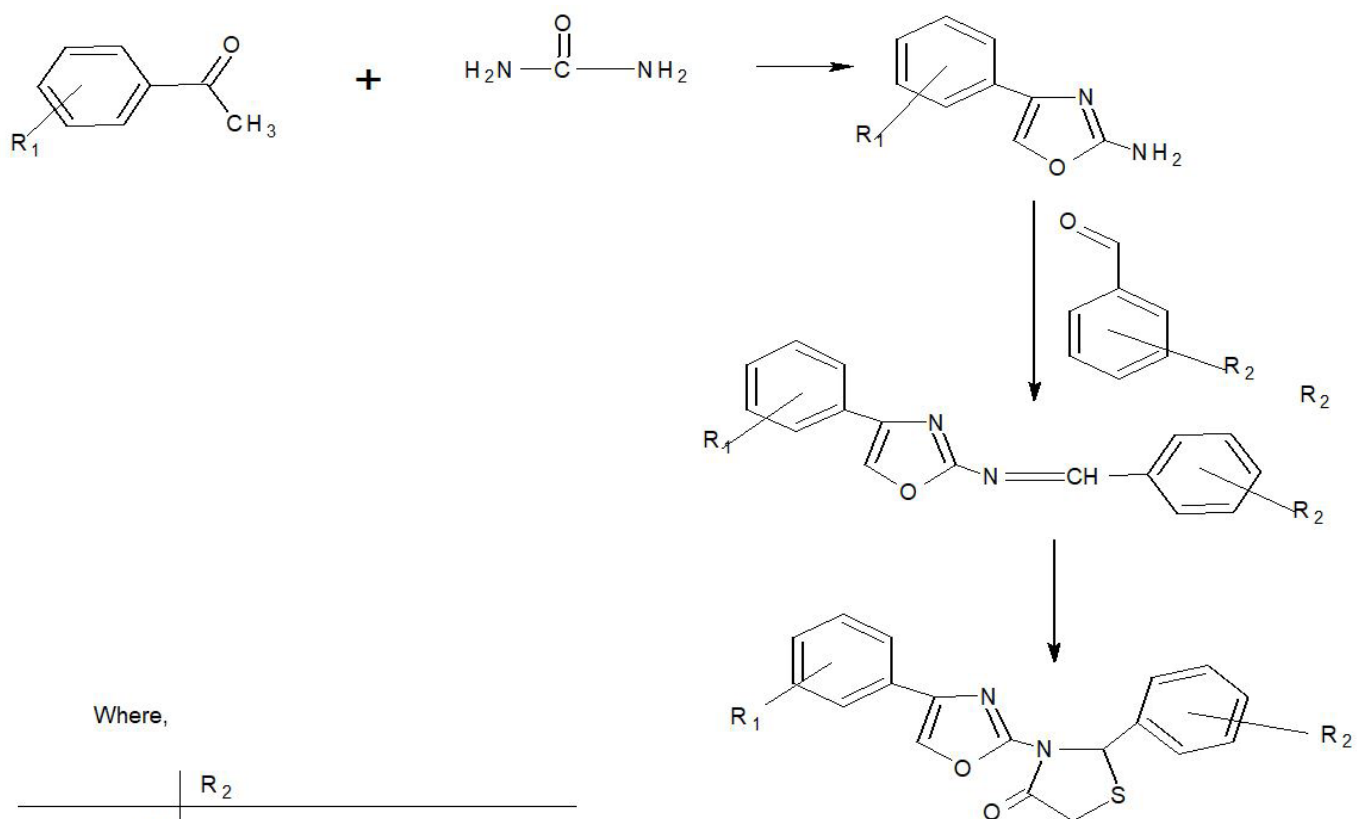
## Result And Discussion

In light of these findings, various compounds containing 2-amino, 4-substituted phenyl thiazole, and 2-substituted phenyl imine were synthesized. Moiety has been connected to 4-substituted phenyl thiazole, 2-substituted aryl, 3-substituted phenyl thiazole, and 4-thiazolidinones.

Scheme-1 depicts the chemical sequence that leads to the synthesis of required heterocyclic compounds. By reacting substituted acetophenone with thiazole in the presence of Br<sub>2</sub> - H<sub>2</sub>O and ethanol, the starting material 2-amino, 4-substituted phenyl thiazole (1a-o) was created. 2-Amino-substituted phenyl synthesis 2-[4-oxo-2-substituted aryl-Thiazolidinyl] substituted 4-substituted phenyl thiazole (2a-o) The IR, H1 NMR, C<sup>13</sup>NMR, and Mass spectra of the 2-substituted aryl-3substituted phenyl thiazole 4-thiazolidinones were obtained by reacting 2-amine substituted phenyl, 4-substituted phenyl thiazole with thioglycolic acid and zinc chloride in the presence of benzene.

## Biological Studies

Norfloxacin and Griseofulvaline were used as standards in a biological study of thiourea with various acetophenones and (3a-o). The biological activity of compound (1) has been found to be higher than that of the freshly synthesised (3a-o). For antibacterial and antifungal screening, the synthesised compounds were tested against staphylococcus aureus, *E. coli*, *P. vulgaris*, *A. niger*, *B. substillis*, and *Candida albicans* at a concentration of 100 mL as shown in Table 1.



Where,

	R <sub>2</sub>
1)	H
2)	2-OH
3)	3-OH
4)	4-OH
5)	2-NO <sub>2</sub>
6)	3-NO <sub>2</sub>
7)	4-NO <sub>2</sub>
8)	2-CL
9)	3--CL
10)	3-OCH <sub>3</sub>
11)	4-OCH <sub>3</sub>
12)	3, 4, 5-(OCH <sub>3</sub> ) <sub>3</sub>
13)	-N(CH <sub>3</sub> ) <sub>2</sub>
14)	2-Br
15)	4-Br

Scheme 1

Table 1: Antibacterial and Antifungal activities of compounds 3a-o

Compounds	<i>S. aureus</i>	<i>B. substills</i>	<i>E. coli</i>	<i>C. albicans</i>	<i>A. niger</i>
3a	+	+++	+	++	++
3b	++	++	+++	+++	++
3c	+	++	+++	++	++
3d	—	+++	+	+++	+++
3e	+++	++	++	+++	++
3f	++	+++	—	++	++
3g	+++	—	+	—	+++
3h	++	+	+++	++	—
3i	—	+++	+	+++	+++
3j	—	+++	+	+++	+++
3k	+++	++	++	+++	++
3l	++	+++	—	++	++
3m	+++	—	+	—	+++
3n	++	+	+++	++	—
3o	—	+++	+	+++	+++

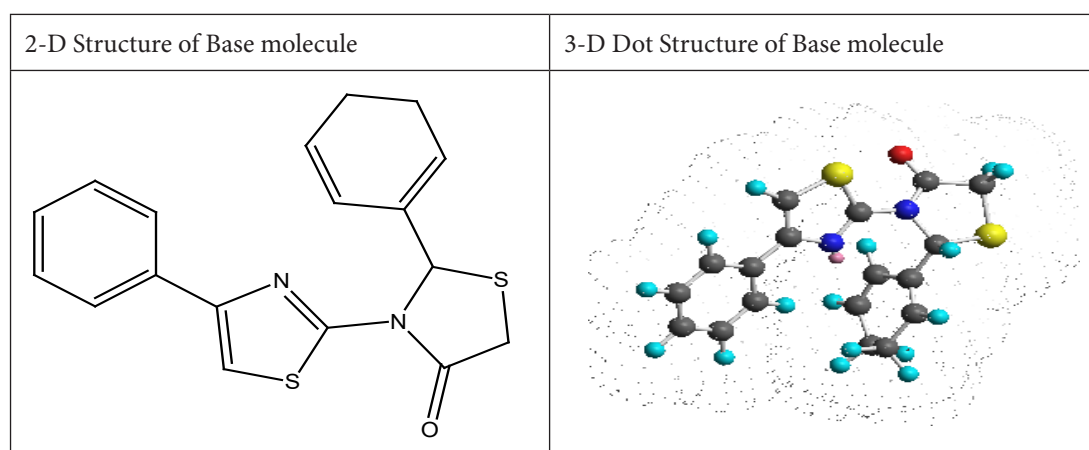
SM (streptomycin) and G F (Griseofulvin). The inhibition diameter in

Mm (-) < 6, (+) 7-9, (++) 10-15, (+++) 16-22, (++++) 23-28

Table 2: Characterization data of newly synthesized 2-[4 oxo-2-substituted-aryl Thiazolidinyl] substituted phenyl thiazole 3(a-o)

Comp	R*	Mol. Formula	Mol. Wt (gm)	M.Pt (C°)	RF Value	% Yield	Analysis found (Cal) %		
							C	H	N
3a	H	C <sub>18</sub> H <sub>14</sub> O <sub>2</sub> N <sub>2</sub> S	322	165	0.91	83	67.08	4.34	8.69
							67.0	4.33	8.11
3b	2-OH	C <sub>17</sub> H <sub>16</sub> O <sub>2</sub> N <sub>2</sub> S	338	172	0.72	79	63.90	4.14	7.62
							63.2	4.74	7.43
3c	3-OH	C <sub>17</sub> H <sub>16</sub> O <sub>2</sub> N <sub>2</sub> S	338	181	0.75	75	63.90	4.14	7.62
							63.2	4.74	7.43
3d	4-OH	C <sub>17</sub> H <sub>16</sub> O <sub>2</sub> N <sub>2</sub> S	338	188	0.82	58	63.90	4.14	7.62
							63.2	4.74	7.43
3e	2-NO <sub>2</sub>	C <sub>18</sub> H <sub>13</sub> O <sub>4</sub> N <sub>3</sub> S	367	191	0.77	54	58.85	3.54	11.4
							58.84	3.41	11.0
3f	3-NO <sub>2</sub>	C <sub>18</sub> H <sub>13</sub> O <sub>4</sub> N <sub>3</sub> S	367	191	0.77	54	58.85	3.54	11.4
							58.84	3.41	11.0
3g	4-NO <sub>2</sub>	C <sub>18</sub> H <sub>13</sub> O <sub>4</sub> N <sub>3</sub> S	367	191	0.77	54	58.85	3.54	11.4
							58.84	3.41	11.0
3h	2-CL	C <sub>18</sub> H <sub>13</sub> O <sub>2</sub> N <sub>2</sub> SCI	356	161	0.75	56	60.67	3.65	7.86
							60.2	3.62	7.54

<b>3i</b>	4-CL	$C_{18}H_{13}O_2N_2S$	356	161	0.75	56	60.67	3.65	7.86
							60.2	3.62	7.54
<b>3j</b>	3-OCH <sub>3</sub>	$C_{19}H_{16}O_3N_2S$	352	144	0.66	66	64.77	4.54	7.9
							64.2	4.20	7.54
<b>3k</b>	4-OCH <sub>3</sub>	$C_{19}H_{16}O_3N_2S$	352	144	0.66	66	64.77	4.54	7.9
							64.2	4.20	7.54
<b>3l</b>	3-(OCH <sub>3</sub> ) <sub>3</sub>	$C_{21}H_{20}O_3N_2S$	380	138	0.73	68	66.31	5.26	7.36
							66.0	5.20	7.33
<b>3m</b>	-N(CH <sub>3</sub> ) <sub>2</sub>	$C_{20}H_{19}O_2N_3S$	365	172	0.77	62	65.75	5.20	11.5
							56.03	5.20	11.4
<b>3n</b>	2-Br	$C_{18}H_{13}O_2N_2SBr$	391	163	0.73	59	55.24	3.32	7.16
							55.22	3.20	7.54
<b>3o</b>	4-Br	$C_{18}H_{13}O_2N_2SBr$	391	163	0.73	59	55.24	3.32	7.16
							55.22	3.20	7.54



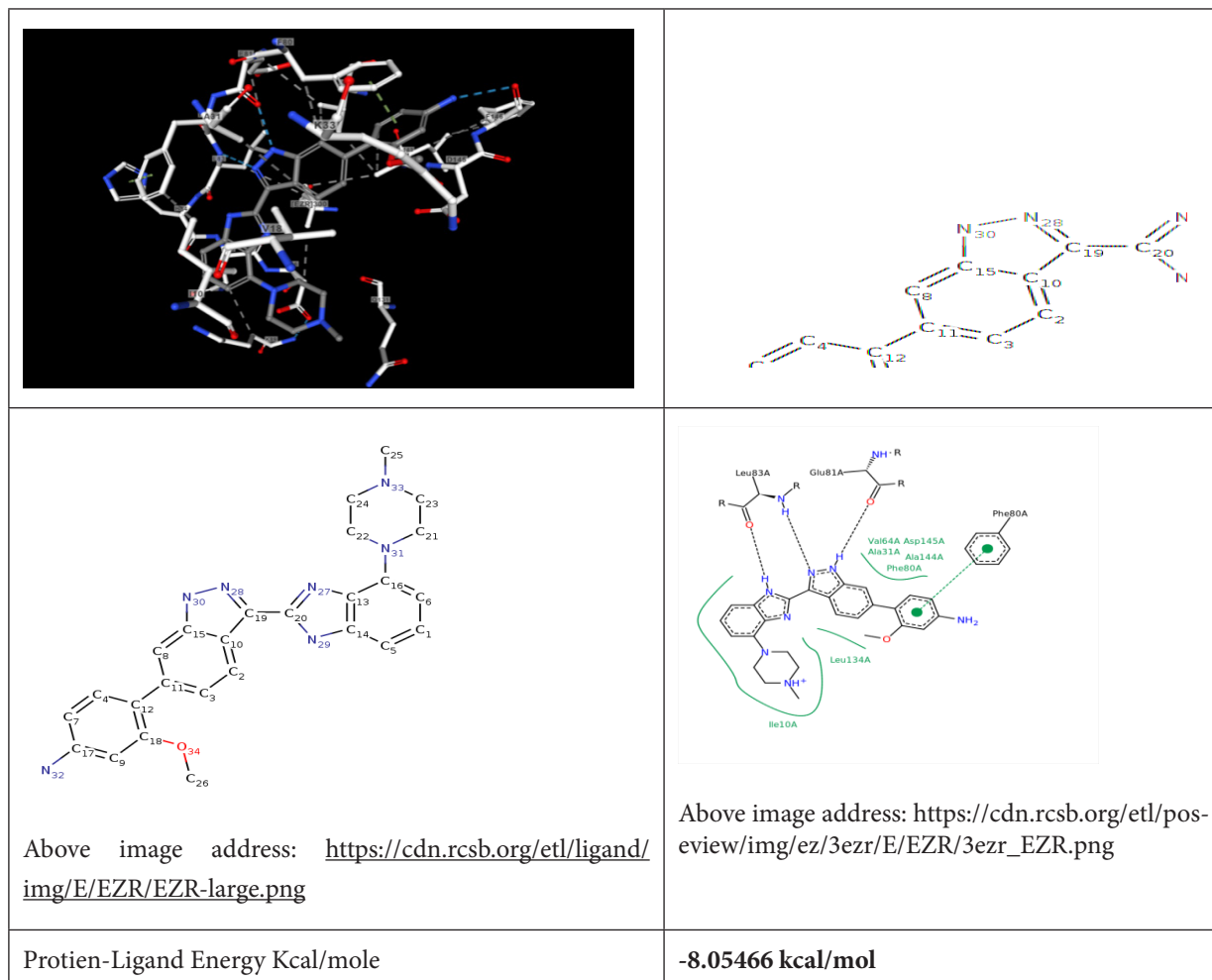
**Figure 1:** Base molecule 2-Cyclohexa-1,5-diphenyl-4-phenyl-[2,3'] bithiazolyl-4'-one

**Table 3:** IR, <sup>1</sup>H NMR & <sup>13</sup>C NMR of newly synthesized 3(a-o)

compounds	IR(KBr)	<sup>1</sup> H NMR (300MHz DMSO)	<sup>13</sup> C NMR (300MHz, DMSO-d <sub>6</sub> )
<b>3a</b>	2945 (C-H Aromatic stretch) 1791.8, 1713, 1641, 1520, 779 (C-S)	9.53 (S1H NH)	14.2,13.1,13.6,23.0,37.9,38.2, 34.5,39.4,40.0,58.5,76.8,7.3,111. 8,159.1,126.2,137.3,160.2,162.1.
<b>3b</b>	2945 (C-H Aromatic stretch), 3275 (OH of phenyl ring) 1639 & 1655 cyclic carbonyl ring, 690 (C-S-C linkage of thiazolidinone ring), 1152 (C-O str) 3209 (N-H Stretch) 1791.8, 1713, 1641, 1520, 779 (C-S);	2.24, 4.23, 3.56 6.8-7.8 (M.8H Aromatic proton) 3.5 (s, 2H, CH <sub>2</sub> Thiazolidine ring)	14.1, 13.0, 13.62, 23.1, 37.9, 38. 0, 34.1, 39.2, 40.1, 58.3, 72.3, 7.3, 111.5, 159.1, 126.0, 137.1, 160.2, 162.1.

<b>3c</b>	2945 (C-H Aromatic stretch) 3272(OH of phenyl ring) 1637 & 1653 cyclic carbonyl ring,693(C- S-C linkage of thiazolidinone ring),1151 (c-o str)3208 (N-H Stretch) 1791.8,1713,1641,1520,779 (C-S);	2.24,4.21,3.54 6.8-7.8(M.8H Aromatic proton)3.4(s,2H,CH <sub>2</sub> Thiazolidine ring)	14.2,13.1,13.2,23.0,37.8,38.1,34.2,39. 4,40.1,58.5,76.5,7.3,111.3,159.2,126. 1,137.32,160.2,162.2.
<b>3d</b>	2945 (C-H Aromatic stretch) 3274(OH of phenyl ring) 1638 & 1650 cyclic carbonyl ring,691(C- S-C linkage of thiazolidinone ring),1150 (c-o str) 3207(N-H Stretch) 1791.8,1713,1641,1520,779(C-S)	2.25,4.20,3.52 6.8-7.8(M.8H Aromatic proton)3.3(s,2H,CH <sub>2</sub> Thiazolidine ring)	14.2,13.1,13.6,23.0,37.9,38.2,34.5,39. 4,40.0,58.5,76.8,7.3,111.8,159.1,126. 2,137.3,160.2,162.1.
<b>3e</b>	2945 (C-H Aromatic stretch)1791.8, 1713, 1641, 1520, 779(C-S)	2.22,4.20,3.51 6.8-7.8(M.8H Ar- omatic proton)3.3(s, 2H,CH <sub>2</sub> Thiazolidine ring)	14.2, 13.1, 13.2, 23.1, 37.9, 38.1, 34.2, 39.4, 40.0, 58.1, 76.8, 7.3, 111.2, 159.0, 126.1, 137.3, 160.1, 162.1.
<b>3f</b>	2945 (C-H Aromatic stretch)1791.8, 1713, 1641, 1520, 779 (C-S)	2.20,4.21,3.54m, 6.8-7.8(M.8H Aromatic proton) 3.3( s, 2H, CH <sub>2</sub> Thiazolidine ring)	14.1, 13.2, 13.0, 23.0, 37.9, 38.1, 34.5, 39.2, 40.0, 58.2, 76.8, 7.3, 111.2, 159.1, 126.2, 137.3, 160.2, 162.1.
<b>3g</b>	2942 (C-H Aromatic stretch) 1791.8, 1713, 1641, 1520, 779 (C-S)	2.24,4.23,3.56 6.8-7.8 (M.8H Aromatic proton)3.4 (s,2H,CH <sub>2</sub> Thiazolidine ring)	14.0,13.1,13.6,23.1,37.9,38.0, 34.5, 39.4, 40.0, 58.2,76.2,7.3,111.3,159.1, 126.1,137.2,160.2,162.1.
<b>3h</b>	2944 (C-H Aromatic stretch) 1791.8,1713,1641,1520,779(C-S); 1689(C=O) of thiazolidinone ring	2.24, 4.23, 3.56 6.5-7.8 (M.8H Aromatic proton) 3.3 ( s, 2H, CH <sub>2</sub> Thiazolidine ring)	14.0,13.2,13.6,23.0,37.9,38.2,34.2,39. 1,40.0,58.5,76.2,7.3,111.3,159.1,126. 2,137.3,160.2,162.1.
<b>3i</b>	2941 (C-H Aromatic stretch) 1791.8, 1713, 1641, 1520, 779 (C-S);	2.24, 4.23, 3.56, 6.7-7.8 (M.8H Aromatic proton) 3.3 (s, 2H, CH <sub>2</sub> Thiazolidine ring)	14.2,13.1, 13.5, 23.1, 37.9, 38.2, 34.5, 39.4, 40.1, 58.5,76.8,7.3,111.8,159.1, 126.2,137.3,160.2,162.1.
<b>3j</b>	2945 (C-H Aromatic stretch),3275(OH of phenyl ring) 1639 & 1655 cy- clic carbonyl ring,690 (C-S-C link- age of thiazolidinone ring),1152 (c-o str)3209 (N-H Stretch) 1791.8,1713,1641,1520,779(C-S);	2.24,4.23,3.56 6.8-7.8 (M.8H Aromatic proton) 3.5 (s,2H,CH <sub>2</sub> Thiazolidine ring)	14.1,13.0,13.62,23.1,37.9,38.0,34.1,3 9.2,40.1,58.3,72.3,7.3,111.5,159.1,12 6.0,137.1,160.2,162.1.
<b>3k</b>	2945 (C-H Aromatic stretch) 3272(OH of phenyl ring) 1637 & 1653 cyclic carbonyl ring,693(C- S-C linkage of thiazolidinone ring),1151 (c-o str)3208 (N-H Stretch) 1791.8,1713,1641,1520,779(C-S)	2.24,4.21,3.54 6.8-7.8(M.8H Aromatic proton)3.4(s,2H,CH <sub>2</sub> Thiazolidine ring)	14.2,13.1,13.2,23.0,37.8,38.1,34.2,39. 4,40.1,58.5,76.5,7.3,111.3,159.2,126. 1,137.32,160.2,162.2.
<b>3l</b>	2945 (C-H Aromatic stretch) 3274(OH of phenyl ring) 1638 & 1650 cyclic carbonyl ring,691(C- S-C linkage of thiazolidinone ring),1150 (c-o str) 3207(N-H Stretch) 1791.8,1713,1641,1520,779(C-S)	2.25,4.20,3.52 6.8-7.8(M.8H Aromatic proton)3.3(s,2H,CH <sub>2</sub> Thiazolidine ring)	14.2,13.1,13.6,23.0,37.9,38.2,34.5,39. 4,40.0,58.5,76.8,7.3,111.8,159.1,126. 2,137.3,160.2,162.1

<b>3m</b>	2945 (C-H Aromatic stretch)1791.8, 1713, 1641, 1520, 779(C-S)	2.22,4.20,3.51 6.8-7.8(M.8H Aromatic proton)3.3(s, 2H,CH <sub>2</sub> Thiazolidine ring)	14.2, 13.1, 13.2, 23.1, 37.9, 38.1, 34.2, 39.4, 40.0, 58.1, 76.8, 7.3, 111.2, 159.0, 126.1, 137.3, 160.1, 162.1
<b>3n</b>	2945 (C-H Aromatic stretch)1791.8, 1713, 1641, 1520, 779 (C-S)	2.20,4.21,3.54m, 6.8-7.8(M.8H Aromatic proton) 3.3( s, 2H, CH, Thiazolidine ring)	14.1, 13.2, 13.0, 23.0, 37.9, 38.1, 34.5, 39.2, 40.0, 58.2, 76.8, 7.3, 111.2, 159.1, 126.2, 137.3, 160.2, 162.1
<b>3o</b>	2942 (C-H Aromatic stretch) 1791.8, 1713, 1641, 1520, 779 (C-S)	2.24,4.23,3.56 6.8-7.8 (M.8H Aromatic proton)3.4 (s,2H,CH <sub>2</sub> Thiazolidine ring)	14.0,13.1,13.6,23.1,37.9,38.0, 34.5, 39.4, 40.0, 58.2,76.2,7.3,111.3,159.1, 126.1,137.2,160.2,162.1



**Figure 2:** Natural Inhibitor 3-methoxy-4-{3-[4-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-indazol-6-yl} aniline of PDB ID 3EZR [9,10]

### Function of CDK Activities

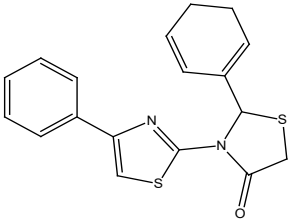
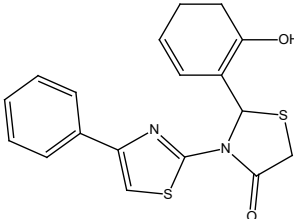
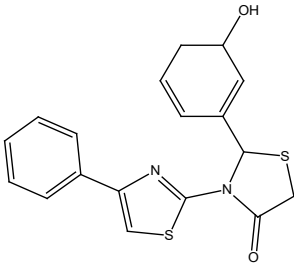
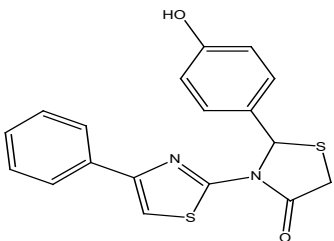
In the protein databank, there exist a lot of CDK2 electronic structures<sup>11</sup>. Because of the existence of a natural inhibitor in one of the key active sites, 3EZR was chosen. This structure is also comprehensive and error-free. Inhibition of cyclin A and cyclin E-associated cyclin-dependent kinase-2 (CDK2) activity in tumour cells is an effective technique to induce apoptotic cell death via the E2F pathway. The cyclin groove recognition

motif (CRM) in the CDK-inhibitory (CDKI) tumour suppressor protein p27 KIP1 was used to develop and synthesise a series of cyclic peptides with biological activity and structural characterization by NMR and X-ray crystallography<sup>12</sup>. Inhibitors of cyclin-dependent kinases (Cdk) have been shown to block Cdk7 and Cdk9, which control transcription, in chronic lymphocytic leukaemia cells. Here we studied the novel Cdk inhibitor SNS-032, which exhibits potent and selective inhibitory activity

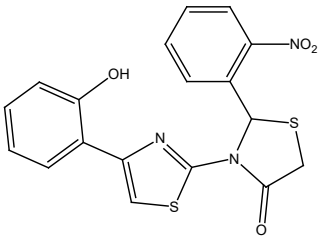
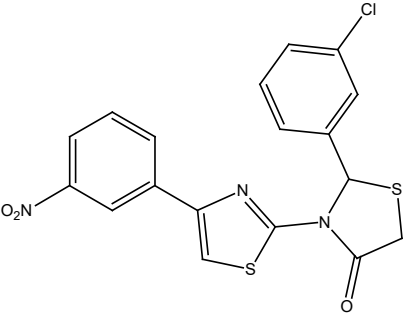
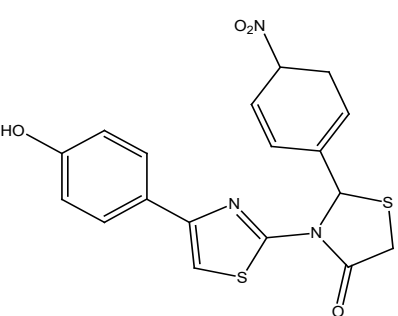
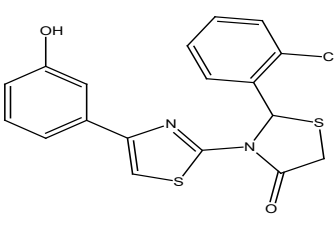


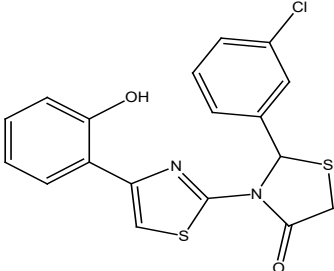
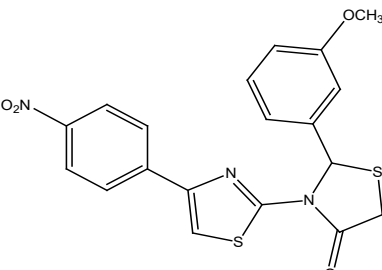
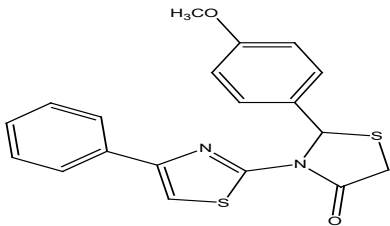
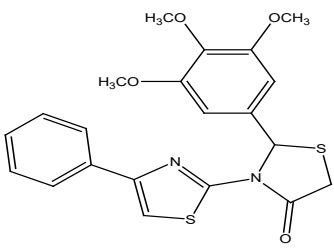
against Cdk2, Cdk7, and Cdk9<sup>13</sup> Overexpression of cyclooxygenase-2 (COX-2) is frequently observed in several human cancers, including lung, colon, and head and neck. Malignancies are also associated with the dysregulation of cell cycle events and concomitant elevated activity of cyclin-dependent kinases (CDK).

CDK2 is a key cell cycle regulatory protein that controls the transition of cells from G1 to S phase. By suppressing CDK2 activity in the H358 human non-small cell lung cancer cell line, we provide many lines of evidence that demonstrate a functional role for CDK2 in IL-1-induced COX-2 expression [14].

Sr.NO.	2-Dimentional Structure	R2
1	 <p data-bbox="279 705 1018 750">2'-Cyclohexa-1,5-dienyl-4-phenyl-[2,3']bithiazolyl-4'-one</p> <p data-bbox="279 795 845 831">Molecular formula : C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>, Exact mass: 340.07</p>	-H
2	 <p data-bbox="279 1086 1184 1131">2'-(2-Hydroxy-cyclohexa-1,5-dienyl)-4-phenyl-[2,3']bithiazolyl-4'-one</p> <p data-bbox="279 1176 853 1211">Molecular formula : C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>, Exact mass: 356.07</p>	2-OH
3	 <p data-bbox="279 1512 1184 1556">2'-(3-Hydroxy-cyclohexa-1,5-dienyl)-4-phenyl-[2,3']bithiazolyl-4'-one</p> <p data-bbox="279 1601 853 1637">Molecular formula : C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>, Exact mass: 356.07</p>	3-OH
4	 <p data-bbox="279 1915 1098 1960">2-(4-hydroxyphenyl)-3-(4-phenylthiazol-2-yl)thiazolidin-4-one</p> <p data-bbox="279 2004 853 2040">Molecular formula : C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>, Exact mass: 354.05</p>	4-OH



5	 <p>3-(4-(2-hydroxyphenyl)thiazol-2-yl)-2-(2-nitrophenyl)thiazolidin-4-one <math>M_o</math>-  molecular formula : <math>C_{18}H_{13}N_3O_4S_2</math> Exact mass: 399.03</p>	2-NO <sub>2</sub>
6.	 <p>2-(3-chlorophenyl)-3-(4-(3-nitrophenyl)thiazol-2-yl)thiazolidin-4-one  Molecular formula : <math>C_{18}H_{12}ClN_3O_3S_2</math> Exact mass: 417.00</p>	3-Cl,-3NO2
7	 <p>3-(4-(4-hydroxyphenyl)thiazol-2-yl)-2-(4-nitrocyclohexa-1,5-dien-1-yl)thiazolidin-4-on  e  Molecular formula : <math>C_{18}H_{15}N_3O_4S_2</math> Exact mass: 401.05</p>	4-NO <sub>2</sub> , 4-OH
8	 <p>2-(2-chlorophenyl)-3-(4-(3-hydroxyphenyl)thiazol-2-yl)thiazolidin-4-one  Molecular formula : <math>C_{18}H_{13}ClN_2O_2S_2</math> Exact mass: 388.01</p>	2-Cl

9*	 <p>2-(3-chlorophenyl)-3-(4-(2-hydroxyphenyl)thiazol-2-yl)thiazolidin-4-one</p> <p>Molecular formula : <math>C_{18}H_{13}ClN_2O_2S_2</math> Exact mass: 388.01</p>	3-Cl
10	 <p>2-(3-methoxyphenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one</p> <p>Molecular formula : <math>C_{19}H_{15}N_3O_4S_2</math> Exact mass: 413.05</p>	3-(OCH <sub>3</sub> ),
11	 <p>2-(4-methoxyphenyl)-3-(4-phenylthiazol-2-yl)thiazolidin-4-one</p> <p>Molecular formula : <math>C_{19}H_{16}N_2O_2S_2</math> Exact mass: 368.07</p>	4-OCH <sub>3</sub>
12	 <p>3-(4-phenylthiazol-2-yl)-2-(3,4,5-trimethoxyphenyl)thiazolidin-4-one</p> <p>Molecular formula : <math>C_{21}H_{20}N_2O_4S_2</math> Exact mass: 428</p>	3,4,5-(OCH <sub>3</sub> ) <sub>3</sub>

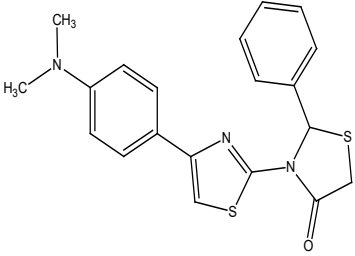
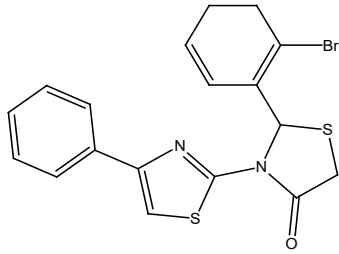
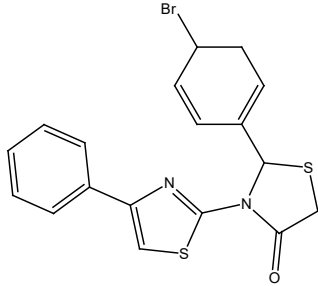
13	 <p>3-(4-(4-(dimethylamino)phenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one</p> <p>Molecular formula : C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>OS<sub>2</sub>, Exact mass: 381.10</p>	4-N(CH <sub>3</sub> ) <sub>2</sub> ,
14	 <p>2'-(2-Bromo-cyclohexa-1,5-dienyl)-4-phenyl-[2,3']bithiazolyl-4'-one</p> <p>Molecular formula : C<sub>18</sub>H<sub>15</sub>BrN<sub>2</sub>OS<sub>2</sub>, Exact mass: 419.36</p>	2-Br
15	 <p>2'-(4-Bromo-cyclohexa-1,5-dienyl)-4-phenyl-[2,3']bithiazolyl-4'-one</p> <p>Molecular formula : C<sub>18</sub>H<sub>15</sub>BrN<sub>2</sub>OS<sub>2</sub>, Exact mass: 419.36</p>	4-Br

Figure 3: Substituted 2-Cyclohexa-1,5-dienyl-4-phenyl-[2,3] bithiazolyl-4-one

Molecular docking techniques are used to test fifteen molecules of 2-Cyclohexa-1, 5-diphenyl-4-phenyl-[2, 3'] bithiazolyl-4'-one for their ability to inhibit CDK2 (PDB ID 3EZR) enzyme. The goal is to look at the binding energies, different interaction postures, and probable hydrogen bonding of these compounds in order to better understand how efficient they are as CDK inhibitors, specifically CDK2 inhibitors.

### Synthesized molecules (Ligand)

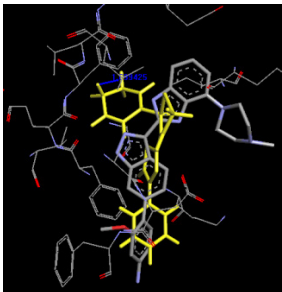
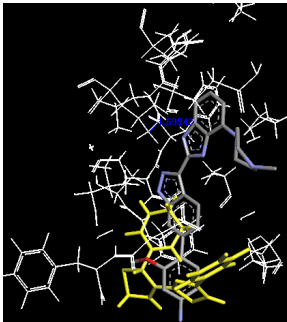
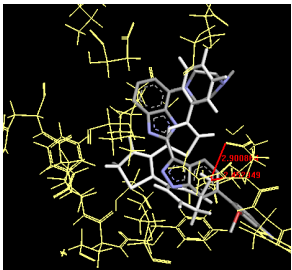
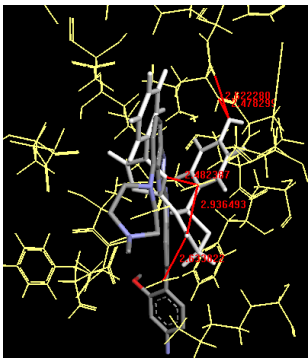
Table 4 listed fifteen compounds that were chosen to explore enzyme inhibition with manufactured molecules (also known as ligands).

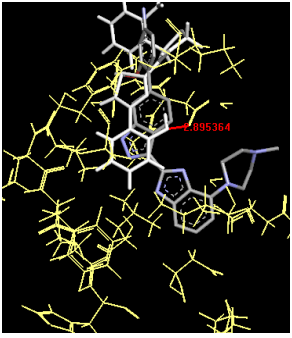
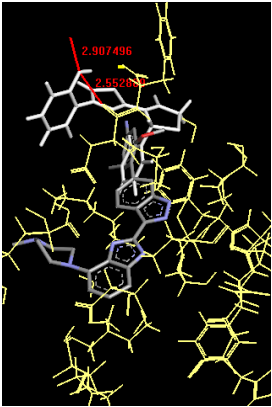
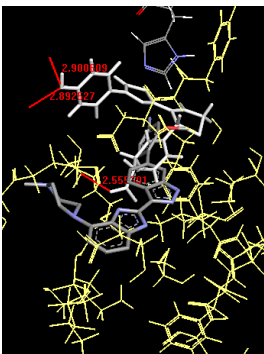
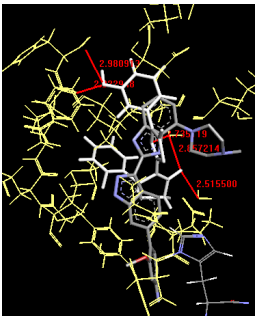
### Receptor enzyme

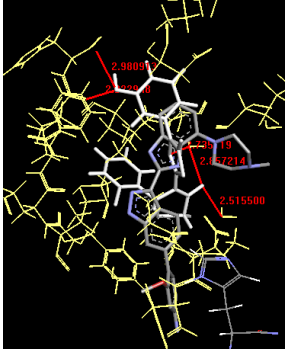
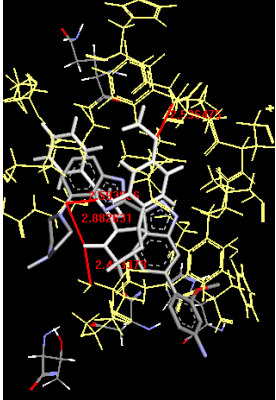
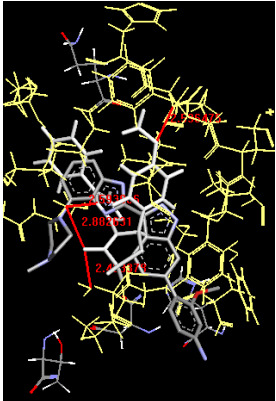
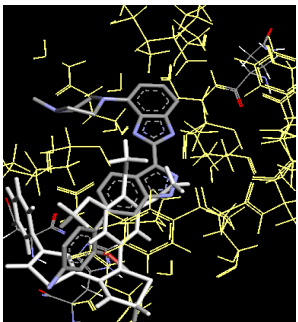
The electronic structure of CDK2, with PDB ID 3EZR, was chosen as a target protein. The protein file was obtained from an online database. 3-methoxy-4-{3-[4-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-indazol-6-yl} As a natural inhibitor, aniline<sup>17</sup>. The chosen enzyme structure was created without any uncertainties, such as missing atoms or amino acids. After removing all heteroatoms (non-receptor atoms like water, ions, and so on), Kollmann charges were assigned. Using AutoDock's Addsol function, the Solvation parameters were added to the final macromolecule structure<sup>18</sup>. The natural inhibitory

site in an enzyme is considered as the active site of a chosen enzyme and used without further processing.

**Table 4:** Lists obtained binding energies for all docked molecules

	Surface Dot 3-D structure	Binding Energy In Kcal/mole	H-bond distance	Amino acids
1*		-11.6863	2.744652	955-DEF 145-ASP 955- DEF 82-PHE 80-PHE 33-LYS
2		-10.7636		958- DEF
3		-10.0056	2.452949 2.900864	145 -ASP
4		-10.0197	2.633822 2.936493 2.482387 2.62280 2.478299	83-LEU

5		-10.0197	2.895364	145- ASP
6		-10.3206	2.907496 2.552889	125 -HIS 145- ASP
7		-9.84859	2.555301, 2.892527, 2.900609A	14 -THR 127 -ASP
*8		-11.0653	2.980913A 2.22294A 2.735119A ,2.857214 A 2.5155	85 - G L - N,85-LEU

9				
10		-9.62396	,2.59475 ,2.593906 ,2.882631 .2.493378	83-LEU
11		-9.62396	,2.59475 ,2.593906 ,2.882631 .2.493378	83-LEU
12		-10.7636	---	





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