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# CHEMICAL INHIBITOR FOR TANKYRASE 1 TO CONTROL CELL PROLIFERATION IN CANCER

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Telomeres are repeated TTAGGG sequences that stop natural chromosome ends from behaving as random breaks, tankyrase 1 upregulation, decrease the TRF1-TIN2-TPP1-POT1 loading on a chromosome end, attenuates the impact of telomerase inhibitors by allowing access of residual telomerase activity. Conversely, blockade of tankyrase1 enhances the effect of telomerase inhibitors, whereas tankyrase1 removes the telomeric protein complex by poly (ADP-ribosyl) ating TRF1. In cancerous cells protein tankyrase1 binds with Trf1 , resulting in degradation of Trf1complex (sheltrin) on telomeres ,which allows telomerase binding on telomere proceeding a un controlled replication , to tackle this we had taken tankyrase1 as a target, PARP domain (PDB ID: 2RF5) of tankyrase1 is responsible for trf1's poly(ADP-ribosyl)ation and degradation of sheltrin in cancerous cells, to inhibit activity of PARP domain docking is performed to find the inhibitors for PARP domain, docking predicted 13 different ligands showing docking with 2RF5, out of these Acetoxy(4-aminophenyl)mercury is predicted best on the basis of its energy and dock score.

**Keywords: Telomere, Sheltrin, Telomerase, Tankyrase 1, PARP**

## INTRODUCTION

The Telomere shortening theory of aging implies that cell death is caused by telomere shortening, during each cell division, the role of telomeres is to assist, complete replication

of eukaryotic chromosomes **[1,2]** and protecting chromosome ends from recombination. Cell with shorter telomeres undergo significantly fewer doublings than those with longer telomeres **[3]**. This shortening of telomeres results in degradation of telomeric region of DNA on each cell division, and at a point of time the cell stops replicating, & it dies off, which eventually leads to death of the entire organism, this phenomenon is termed as end replication problem **[4, 5, 6,7]**.

Telomerase enzyme replaces /repairs shortened telomeres such that the cells are able to replicate (theoretically) forever. These are only discovered in some germs and cancer cells, but not in most normal organisms. If the telomerase gene could be activated or spliced into regular human cells (assuming telomere theory is correct), **[3]** human longevity would be greatly increased.

In contrast cancerous cell possess very high telomerase activity, resulting in complete replication of telomeric region too, due to which cancerous cells never dies and keeps on replicating, if somehow binding of telomerase on telomeres in cancerous cells could be controlled, the rapid and forever division of cells can be checked **[8]**. In tumorous and immortalized cells, telomere shortening is halted through the activation of telomerase, and inhibition of TRF complex formation on telomeres of cancerous cells, TRF1 itself can be inhibited by the poly(ADP-ribose)polymerase (PARP) activity of its interacting partner tankyrase1, **[9]** which abolishes its DNA binding activity in vitro and removes the TRF1 complex from telomeres in vivo.

**Telomere elongation by tankyrase 1:** Telomere elongation by tankyrase1 has an important impact on telomerase inhibitors. For telomere elongation, active telomerase needs to gain access to the telomeric 3'-overhang. The TRF1-TIN2-TPP1-POT1 telomeric protein complex termed as sheltrin or telosome, limits telomerase access **[10]** on telomere, whereas tankyrase1 removes the telomeric protein complex by poly (ADP-ribosyl)ating TRF1 **[11, 12]**. Either telomere shortening or tankyrase 1 upregulation, each of which decreases the TRF1-TIN2-TPP1-POT1 loading on a chromosome end, **[10, 13]** attenuates the impact of telomerase inhibitors by allowing access of residual telomerase activity.

Conversely, blockade of tankyrase 1 enhances the effect of telomerase inhibitors. The relative importance of tankyrase 1 vs. tankyrase 2 **[14, 15]** inhibition remains unclear. Inhibition of tankyrases, may indirectly induce cancer cell senescence by

abrogating telomerase activity. Support for this rational is provided by the finding that tankyrase 1 confers resistance to telomerase inhibitors. Experiments have shown the cells overexpressing tankyrase 1; removes TRF1 from telomere DNA **[11]**; have unchanged telomere length following treatment with the telomerase inhibitor. This drug resistance is reversed by PARP inhibitors, **[16]** which are able to block tankyrase 1 PARP activity.

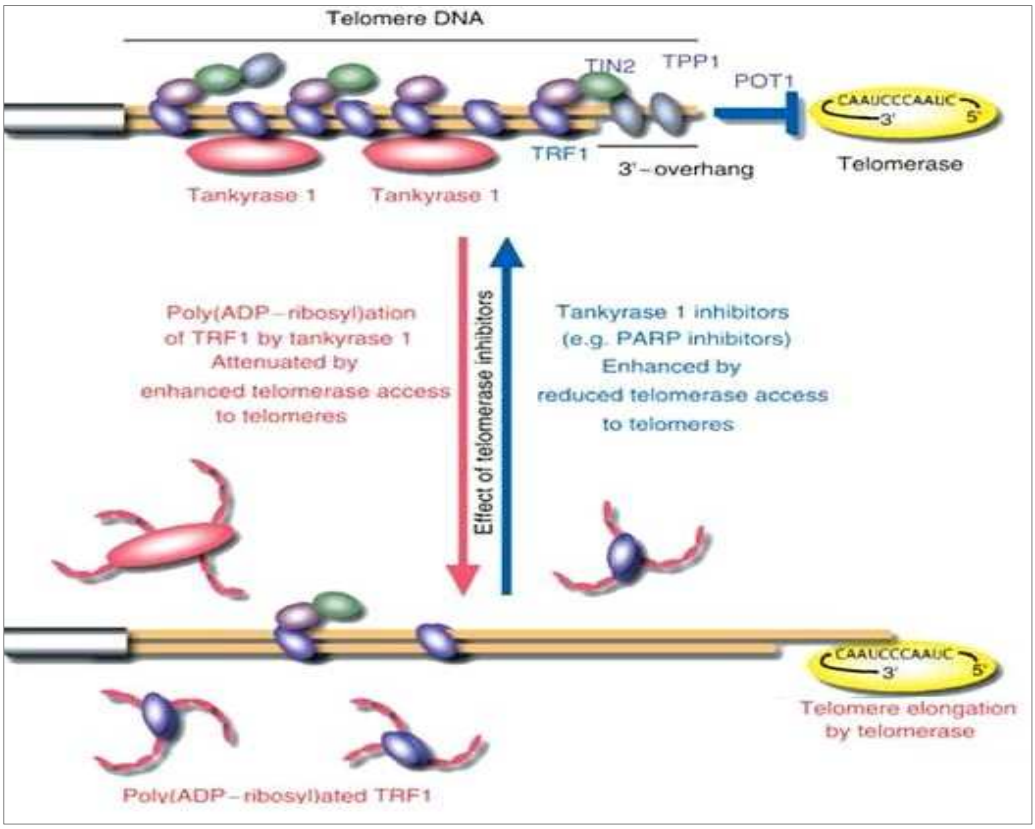



**Figure 1: Degradation of TRF 1 Complex by Tankyrase [11]**

Binding of Sheltrin complex checks telomerase access on telomere, telomerase access can be checked by facilitating sheltrin formation on telomeres. In cancerous cells tankyrase is the protein which degrades the sheltrin complex by poly-ADP ribosilating the TRF1 protein. Inhibition of tankyrase facilitates the sheltrin formation in cancerous cells. This can control the division rate of Cancerous cells.

## MATERIAL AND METHODS

The requirement for the maintenance of telomeres by telomerase by most cancer cells for continued proliferation is a target in

anticancer strategies. Tankyrases are poly (ADP-ribose) polymerases that enhance telomerase access to telomeres. Tankyrase 1 modulates telomerase inhibition in human cancer cells and is reviewed in this report as a potential telomere-directed anticancer target. Structure of PARP domain is already available in PDB (2RF5) **[17]** so there was no need to design structures of complete sequence of tankyrase 1.

After taking Tankyrase 1 as a target 3D structure of the relevant PARP domain was downloaded from PDB and Docking is performed using LigandFit docking Protocol, Structure is typed with CHARMm forcefield which adds Hydrogen atoms where they were missing to fulfill the valancies, then all possible active binding sites are predicted, software predicted 4 active sites out of which 1$^{st}$ one is considered for docking because it was the largest binding site. Now the ligand fit docking of 2RF5 is performed Dock through inbuilt library of chemical compounds, 2RF5 docks with each ligand in library, and suggests best possible ligands on the basis of energies and dock score, Inter molecular Hydrogen bonds are predicted using Discovery studio visualiser.

## RESULTS AND DISCUSSION

In the Docking result, 18 hits were found out of which, molecule No. 4193 (Acetoxy(4-amino phenyl) mercury) has docked in 4 different confirmations, No. 6207 and 13135 has docked in 2 different confirmations. Dock Score and Energies are enlisted in the **Table 1** below.

### Chemical Structures & Composition of Ligand Inhibitors Predicted for PARP Domain

The properties and IUPAC names of ligands were predicted, by the help of ChemDraw tool of ChemSketch. It can predict names as well as physical and chemical properties of chemical compounds for any given structure, takes structure in .smi , .mol , .chk files only.

The ligands obtaind by LigandFit dock are copied in a new 3D-window and saved with .smi extension, these .smi files are then opened in ChemDraw Ultra tool window by selecting open from file menu, once the structure is opened select the complete structure, choose Convert Structure to Name form Structure menu in ChemDraw. Physical and chemical properties were also predicted by ChemDraw, by choosing Show Analysis Window and Show chemical properties window, from view menu of ChemDraw Ultra. The results are shown below in **Table 2.**

### Comparison of Energies and Dock Score

Although the dock score for "N-(furan-2-ylmethyl carbomoyl)-5-nitro thiophene-3-

carboxamode" was more **(Table 3)**, even its energy was also low in comparission to rest of all, but it was showing no bonding with the receptor, hence it was not considered.

Among rest of three "Acetoxy(4-amino phenyl) mercury" was considered as the best result, because with good dock score and energy its showing 2 H-bonds with receptor. Docked result of Acetoxy(4-amino phenyl) mercury **(Figure 2)**.

**Hydrogen bonds between receptor (2rf5_a) and ligand: (acetoxy (4 aminophenyl) mercury)**

Acetoxy(4-amino phenyl) mercury: H18-A:GLY1211:O

A:ASP1198:HN- Acetoxy(4-amino phenyl) mercury: O3

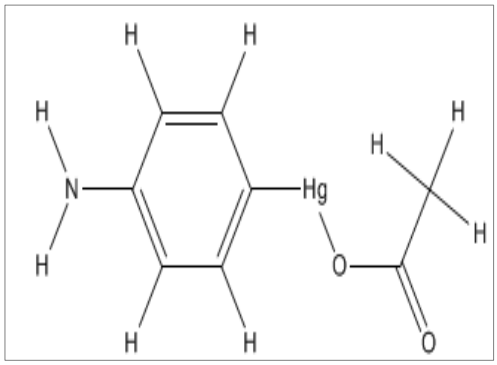
The pharmacological targeting of tankyrase 1 is a potentially significant anticancer strategy if used in conjunction with inhibitors of telomerase. This trend would further promote development not only of telomerase inhibitors but also of PARP inhibitors. In fact, recently, PARP inhibitors have been shown to be very powerful against DNA repair-deficient tumours with the advantage of low cytotoxicity. The inhibition of TRF1 by tankyrase1 is in turn controlled by a second TRF1-interacting factor, TIN2; it protected TRF1 from poly (ADP-ribosyl)ation by tankyrase 1 without affecting tankyrase1 auto modification. Partial knockdown of TIN2 in a telomerase-positive cell line resulted in telomere elongation, which is typical of reduced TRF1 function, this is the case with cancerous cells, hence there are approaches going to inhibit tankyrase1's PARP domain which is responsible for poly (ADP-ribo) sylation of TRF1 in cancer cells **(Figure 2)**.

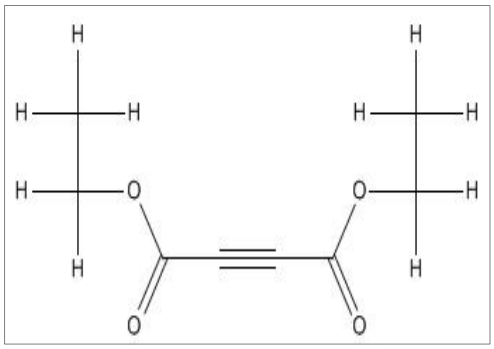
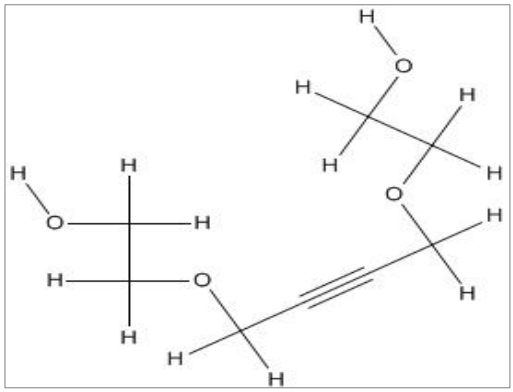
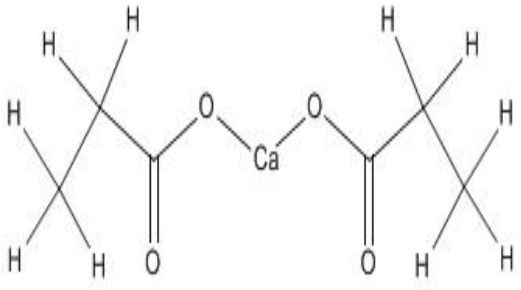
**Table 1: Result of Docking of Receptor Binding Site, with Inbuilt Ligand Library**

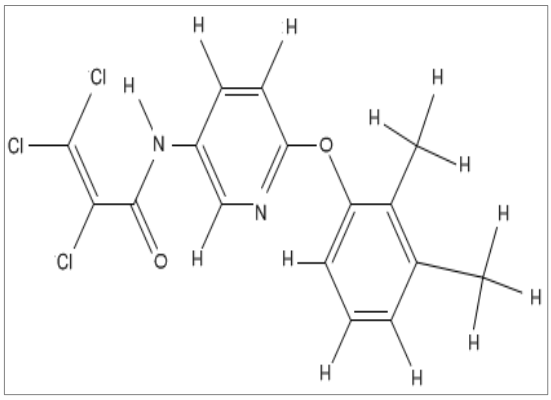
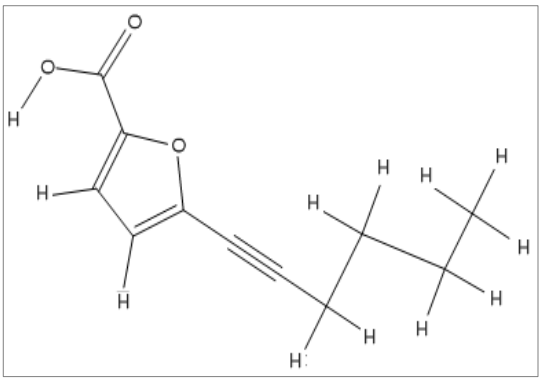
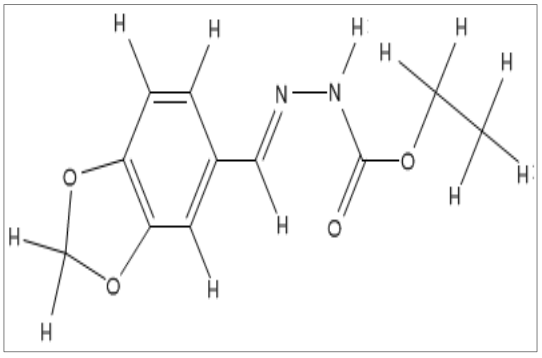
| INDEX | NAME | DOCK SCORE | LIGAND INTERNAL ENERGY | MOLECULAR WEIGHT |
|---|---|---|---|---|
| 1 | Acetoxy(4-amino phenyl) mercury | 17.195 | -0.444 | 351.75 |
| 2 | Acetoxy(4-amino phenyl) mercury | 16.695 | -0.444 | 351.75 |
| 3 | Acetoxy(4-amino phenyl) mercury | 4.342 | -0.444 | 351.75 |
| 4 | Acetoxy(4-amino phenyl)mercury | 1.689 | -0.444 | 351.75 |
| 5 | Diethylebut-2-yne dioate | 15.624 | -0.108 | 170.16 |
| 6 | Diethylebut-2-yne dioate | 15.624 | -0.108 | 170.16 |
| 7 | 2,2'-(but-2-yne-1,4diylbis(oxy)) diethanol | 8.975 | -0.715 | 174.2 |

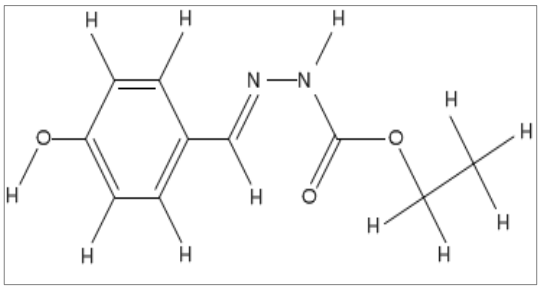
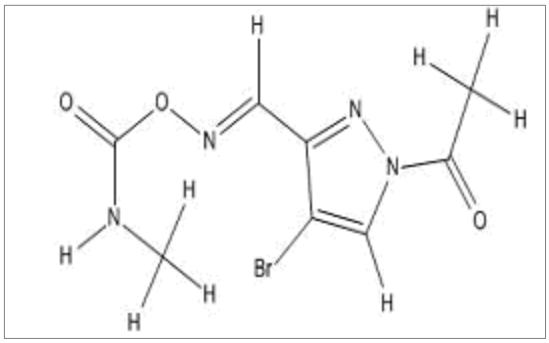
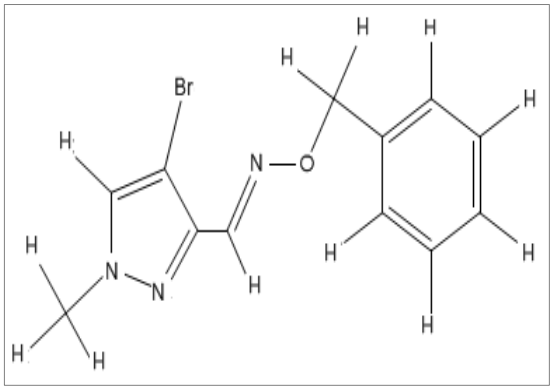
| | | | | |
|---|---|---|---|---|
| **8** | **2,2'-(but-2-yne-1,4-diylbis(oxy)) diethanol** | **7.643** | **-0.715** | **174.2** |
| **9** | **Calcium Propionate** | **5.077** | **-0.117** | **186.22** |
| **10** | **2,3,3-trichloro-N-(6-(2,3-dimethyl phenoxy pyridine-3-yl) acryl amide** | **8.151** | **2.94** | **371.65** |
| **11** | **5-(hex-1-ynyl) furan-2-carboxylic acid** | **2.461** | **-1.328** | **192.21** |
| **12** | **(E)-ethyle 2-benzol[d] [1,3] dioxol-5-yi methylene) hydrazinecarboxylate** | **5.458** | **-1.365** | **236.23** |
| **13** | **(E)-ethyl 2-(4-hydroxylbenzylidene) hydrazine carboxylate** | **2.653** | **-0.844** | **208.22** |
| **14** | **(E)-4-bromo-1-methyl-1H-pyrazole-3-carb aldehyde O-benzyl oxime** | **2.752** | **-0.682** | **289.09** |
| **15** | **(E)-1-acetyl-4-bromo-1H-pyrazole-3-carbaldehyde O-methylcarbamoyl oxime)** | **2.937** | **-2.198** | **294.15** |
| **16** | **(E)-1-((5-(2-chloro-5(tri fluoro methyl) phenyl) furan-2-yl) methylene) -2-(4-fluoro phenyl) hydrazine** | **2.937** | **-2.128** | **294.15** |
| **17** | **N-(furan-2-ylmethyl carbomoyl) -5-nitro thiophene-3-carboxamode** | **20.52** | **-2.572** | **382.74** |
| **18** | **(E)-4-(2-(4-methoxy benzoyl) hydrazinyl) 4-oxobut-2-enoic acid** | **7.722** | **0.887** | **295.27** |

**Table 2: Structure and Chemical Properties of Docked Compounds**

| CHEMICAL PROPERTIES OF THE LIGAND | STRUCTURE OF THE LIGAND |
|---|---|
| **Chemical Formula: $C_8H_9HgNO_2$**<br>**Exact mass: 353.03**<br>**Molecular weight: 351.75**<br>**m/z: 353.03(100.0%),351.03(82.5%),350.03 (59.4%),352.03(51.0%),349.03(33.3%),355.04(23.7%),354.04(9.2%),353.04(4.5%),356.04(2.1%)**<br>**Element Analysis: C,27.32; H,2.58; Hg,57.03; N,3.98; O,9.10**<br>**Smile Notation: O=C(O[Hg]/C1=C(\[H])C ([H])=C(C([H])=C1[H])N([H])[H])C([H]) ([H])[H]**<br>**4193, No. Confirmations Found: 4** |  <br>**Acetoxy(4-aminophenyl) mercury** |
| **Chemical Formula:$C_8H_{10}O_4$**<br>**Exact mass: 170.06**<br>**Molecular weight: 170.16**<br>**Boiling Point: 508.08[K]**<br>**Melting Pont: 370.18[K]**<br>**m/z: 170.06 (100.0%), 171.06(8.9%), 172.06(1.1%).**<br>**Element Analysis: C,56.47; H,3.53;Cl,28.62; N,7.54;** | |

| | |
|---|---|
| **O,8.61**<br>**Smile Notation: O=C(C#CC(=O)OC([H])([H])C([H])([H])[H])OC([H])([H])C([H])([H])[H] 6207, No. Confirmations Found: 2** |  <br>**Diethylebut-2-ynedioate** |
| **Chemical Formula:$C_8H_{14}O_4$**<br>**Exact mass: 174.09**<br>**Molecular weight: 174.19**<br>**Boiling Point: 260.84[K]**<br>**Melting Pont: 451.62[K]**<br>**m/z: 174.09 (100.0%), 175.09(8.8%)**<br>**Element Analysis: C,55.16; H,8.10; O,36.74**<br>**Smile Notation: [H]C([H])(C#CC([H])([H])OC([H])([H])C([H])[H])O[H])OC([H])([H])C([H])([H])O[H] 13135, No. Confirmations Found: 2** |  <br>**2,2'-(but-2-yne-1,4diylbis(oxy)) diethanol** |
| **Chemical Formula:$C_6H_{10}CaO_4$**<br>**Exact mass: 186.2**<br>**Molecular Weight: 186.22**<br>**m/z: 186.02 (100.0%), 187.02(6.6%), 190.01(2.2%), 188.02(1.5%), Element Analysis: C,38.70; H,5.41;Ca,21.52; O,34.37**<br>**Smile Notation: O=C(O[Ca]OC(=O)C([H])([H])C([H])([H])[H])C([H])([H])C([H])([H])[H]13582** |  <br>**Calcium Propionate** |

| | |
|---|---|
| **Chemical Formula:$C_{16}H_{13}Cl_3N_2O_2$**<br>**Exact mass: 370.00**<br>**Molecular weight: 371.65**<br>**Boiling Point: 951.22[K]**<br>**Melting Pont: 676.72[K]**<br>**m/z: 370.00 (100.0%), 372.00(96.0%), 371.01(17.5%), 373.00(17.3%), 375(5.6%), 376.00(3.4%),372.01(1.95), 374.01(1.8%).**<br>**Element Analysis: C,51.71; H,3.53;Cl,28.62; N,7.54; O,8.61**<br>**Smile Notation: O=C(C([Cl])=C([Cl])[Cl] )N([H])C2=C([H])N=C(OC=1C(=C(C([H])=C([H])C=1 [H])C([H])([H])[H])C([H])([H])[H])C([H])=C2[H] 45661** |  <br>**2,3,3-trichloro-N-(6-(2,3-dimethyl phenoxy) pyridine-3-yl)acrylamide** |
| **Chemical Formula:$C_{11}H_{12}O_3$**<br>**Exact mass: 192.08**<br>**Molecular weight: 192.21**<br>**Boiling Point: 660.97[K]**<br>**Melting Pont: 548.2[K]**<br>**m/z: 192.08 (100.0%), 193.08(12.1%)**<br>**Element Analysis: C,68.74; H,6.29; O,24.97**<br>**Smile Notation: =C(O[H])C=1OC(C#CC([H]) ([H])C([H])([H])C([H])([H])C([H])([H])[H])=C([H])C= 1[H] 69637** |  <br>**5-(hex-1-ynyl)furan-2-carboxylic acid** |
| **Chemical Formula:$C_{11}H_{12}N_2O_4$**<br>**Exact mass: 236.04**<br>**Molecular weight: 236.02**<br>**Boiling Point: 738.3[K]**<br>**m/z: 236.08 (100.0%), 237.0812.8%)**<br>**Element Analysis: C,55.93; H,5.12; N,11.86; O,27.09**<br>**Smile Notation: O=C(OC([H])([H])C([H]([H] [H])N([H])N=C([H])C2=C([H])C=1OC([H])([H])OC=1 C([H])=C2[H]70667** |  <br>**(E)-ethyle 2-benzol[d] [1,3]dioxol-5-yimethylene) hydrazine carboxylate** |

| | |
|---|---|
| **Chemical Formula:$C_{11}H_{12}N_2O_4$**<br>**Exact mass: 236.08**<br>**Molecular weight: 236.22**<br>**Boiling Point: 738.3[K]**<br>**m/z: 236.08 (100.0%), 237.08(12.2%)**<br>**Element Analysis: C,55.93; H,5.12 ; N,11.86; O,27.09.**<br>**Smile Notation: O=C(OC([H])([H])C([H])([H])[H])N([H])N=C([H])C1=C([H])C([H])=C(O[H])C([H])=C1[H] 70686** |  <br>**(E)-ethyl 2-(4-hydroxyl benzylidene) hydrazine carboxylate** |
| **Chemical Formula:$C_8H_9BrN_4O_3$**<br>**Exact mass: 287.99**<br>**Molecular weight: 289.09**<br>**Boiling Point: 777.84[K]**<br>**m/z: 287.99 (100.0%), 289.98(97.3%), 290.99(8.7%), 288.98(1.5%), 290.98(1.4%), 289.99(1.1%)**<br>**Element Analysis: C,33.24; H,3.14;Br,27.64; N,19.38; O,16.60**<br>**Smile Notation: O=C(O/N=C(\[H])C1=NN(C([H])=C1[Br])C(=O)C([H])([H])[H])N([H])C([H])([H])[H] 78530** |  <br>**(E)-1-acetyl-4-bromo-1H-pyrazole-3-carbaldehyde O-methylcarbamoyl oxime)** |
| **Chemical Formula:$C_{12}H_{12}BrN_3O$**<br>**Exact mass: 293.02**<br>**Molecular weight: 294.14**<br>**m/z: 293.02(100.0%),295.01(97.3%), 294.02(13.2%), 296.02(12.8%),295.02(1.1%), 296.01(1.1%)**<br>**Element Analysis: C,49.00; H,4.11;Br,27.16 ;N,14.29; O,5.44**<br>**Smile Notation: Br]C=1C(=NN(C=1[H])C([ H])([H])[H])C([H])=NOC([H])([H])C2=C([H])C([H])=C([H])C([H])=C2[H] 78774** |  <br>**(E)-4-bromo-1-methyl-1H-pyrazole-3-carbaldehyde O-benzyl oxime** |

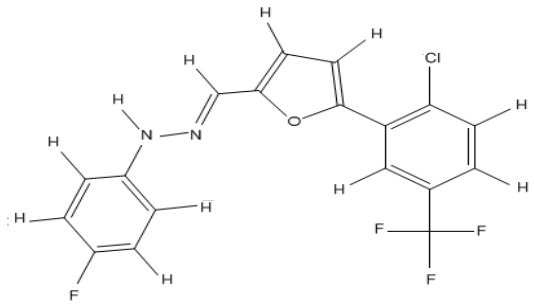
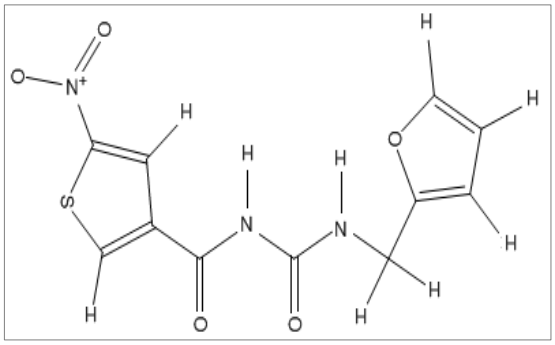
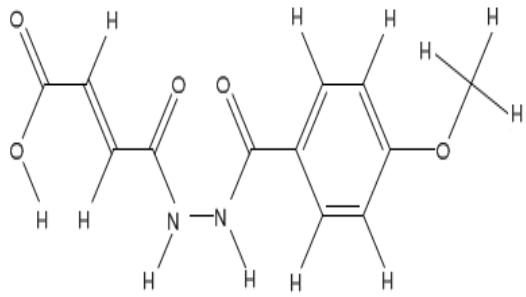
| | |
|---|---|
| **Chemical Formula:$C_{18}H_{11}ClF_4N_2O$**<br>**Exact mass: 382.05**<br>**Molecular weight: 382.04**<br>**Boiling Point: 893.05[K]**<br>**m/z: 382.05(100.0%), 384.05(32.3%), 383.05(20.0%),385.05(6.3%),384.06(1.8%)**<br>**Element Analysis: C,56.49; H,2.90; Cl,9.27;F.19.86;N,7.32; O,4.81**<br>**Smile Notation: [F]C([F])([F])C3=C([H])C(C=2OC(C([H])=NN([H])C1=C([H])C([H])=C([F])C([H])=C1[H])=C([H])C=2[H])=C([Cl])C([H])=C3[H] 90928** |  <br>**(E)-1-((5-(2-chloro-5 (trifluoromethyl) phenyl)furan-2-yl)methylene)-2-(4-lfluorophenyl) hydrazine** |
| **Chemical Formula:$C_{11}H_9N_3O_5S$**<br>**Exact mass: 295.03**<br>**Molecular weight: 295.27**<br>**m/z: 295.03(100.0%), 296.03(13.0%), 297.02(4.5%),297.03(1.9%), 296.02(1.1%)**<br>**Element Analysis: C,44.74; H,3.07; N,14.23; O,27.09;S.10.86**<br>**Smile Notation: [O-][N+](=O)C=2[S]C([H])=C(C(=O)N([H])C(=O)N([H])C([H])([H])C=1OC([H])=C([H])C=1[H])C=2[H] 359820** |  <br>**N-(furan-2-ylmethyl carbomoyl)-5-nitro thiophene-3-carboxamode** |
| **Chemical Formula:$C_{12}H_{12}N_2O_5$**<br>**Exact mass: 264.07**<br>**Molecular weight: 264.23**<br>**Boiling Point: 927.73[k]**<br>**Melting Pont: 773.61[K]**<br>**m/z: 264.07(100.0%),265.08(13.3%), 266.08(1.9%).**<br>**Element Analysis:C,54.55;H,4.58;N,10.60; O,30.28**<br>**Smile Notation: O=C(N([H])N([H])C(=O)C([H])=C([H])C(=O)O[H])C1=C([H])C([H])=C(OC([H])([H])[H])C([H])=C1[H] 368233** |  <br>**(E)-4-(2-(4-methoxybenzoyl) hydrazinyl) 4-oxobut-2-enoic acid** |

**Table 3: Showing Ligands with High Dock Score**

| INDEX | NAME | DOCK SCORE | LIGAND INTERNAL ENERGY |
|---|---|---|---|
| 17 | N-(furan-2-yl methylcarbomoyl) -5-nitro thiophene -3-carboxamode | 20.52 | -2.572 |
| 1 | Acetoxy(4-amino phenyl)mercury | 17.195 | -0.444 |
| 12 | (E)-ethyle 2-benzol [d][1,3] dioxol -5-yi methylene) hydrazinecarboxylate | 5.458 | -1.365 |
| 7 | 2,2-(but-2-yne-1,4 diylbis(oxy)) diethanol | 8.975 | -0.715 |

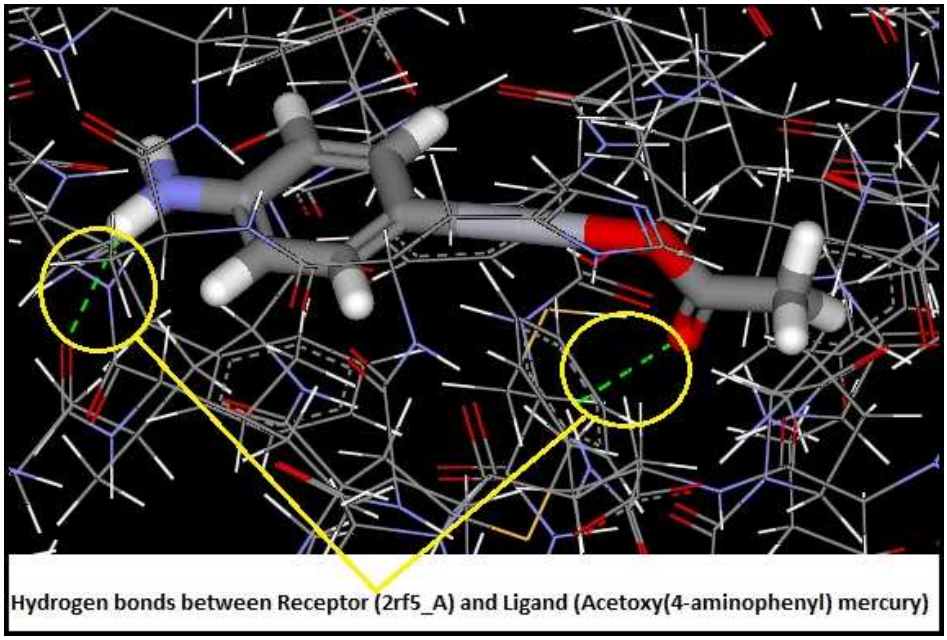



**Figure 2: Showing the Interaction Points Between Receptor (2RF5_A) and Ligand, Green Dotted Lines Show H-bonds Between Acetoxy (4-amino phenyl) Mercury and 2RF5**

## CONCLUSION

In this approach aging mechanism of body is used to put a check on the replication rate of cancerous cells, by going through literature it was found that Tankyrase1 could be very important target in case of cancer, the inhibition of tankyrase1 will facilitates the formation of sheltrin in cancerous cells, which in turn will check the binding of telomerase on telomere controlling the replication of telomeres, leading to degradation of telomere. In this approach we've found a series of inhibitors for PARP domain, by using ligand library, and predicted about 18 ligand compounds showing dock with PARP domain. Their names and properties are

predicted by the help of ChemSketch software. Out of all these ligands, their energy and dock scores were tabulated and 4 best ligands were selected on the basis of their energy and dock score, and the ligand "**Acetoxy (4-amino phenyl) mercury**" was predicted as best docked ligand with **Dock score 17.195**, and E**nergy -0.444.** It showed 2 H-bonds with receptor residues.

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