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High-throughput virtual screening of novel CHK1 inhibitors

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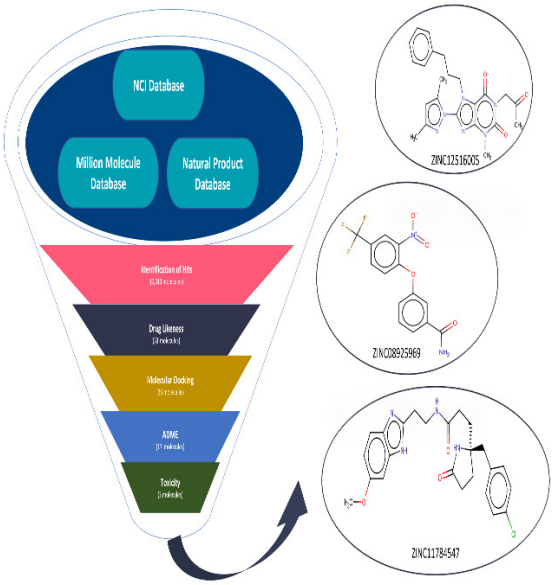
ABSTRACT

Check point kinase 1 (Chk1) is an essential protein in G2 phase checkpoint arrest, which cancer cells need to sustain the cell cycle and prevent cell death. Chk1 inhibitors have been shown to eliminate the S and G2 checkpoints and change the DNA repair pathway, resulting in immature mitotic progression, mitotic catastrophe, and cell death. Normal cells remain in the G1 phase to repair DNA damage as a result of p53 and are less affected by the deletion of the S and G2 checkpoints. Due of its function in this research we have tried to target CHK1 to identify potent CHK1 inhibitors by employing computer aided drug design. Million Molecules Database, Natural Product Database, NCI Database has been screened and three molecules has been identified by structure-based virtual screening followed by filtering for various drug likeness, ADME, toxicity, Molecular docking. Our research work resulted in lead molecules that have shown strong binding affinity with effective ADME properties, low toxicity, and high stability.

Graphical Abstract:



Key words: ewing sarcoma, CHK1, CHK1 inhibitors

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INTRODUCTION

Numerous anticancer treatments induce DNA damage and activate cell cycle checkpoints, giving cancer cells time to repair their DNA and recover [1]. As potential therapeutic targets, these checkpoints have been the subject of extensive research, and Chk1 inhibitors have emerged as fascinating novel therapeutic drugs [2]. Through inactivation of p53 or Rb or amplification of proto-oncogenes, cancer cells usually lack one or more genes for G1 checkpoint regulation (cyclins and CDKs). Chk1 inhibitors that inhibit the remaining checkpoints, S and G2, ought to render cancer cells more susceptible to anticancer therapies, such as c-radiation or DNA-damaging drugs [3-5]. Chk1 was initially recognized as a regulator of the G2/M checkpoint, but it has now been demonstrated to serve other roles in replication fork stability, origin firing, and homologous recombination. Inhibition of these systems can greatly increase the sensitivity of cells to specific antimetabolites [6,7]. Inhibition of CHK-1 is particularly effective in cancer cells devoid of p53 [8]. Consequently, the selective efficacy of CHK-1 inhibitors in combination with cytotoxic, such as DNA-damaging chemicals, is a significant advantage of these medications as cancer therapy [9-11]. Even if several small molecule-based CHK-1 inhibitors are undergoing clinical testing, there is always the possibility of identifying novel CHK1 inhibitors. Using computer-assisted drug design, we have attempted to identify effective CHK1 inhibitors in this study. Million Compounds Database, Natural Product Database, NCI Database has been examined and three molecules has been found by structure-based virtual screening followed by filtering for various drug Likeness, ADME, toxicity, Molecular docking. Our research led to the development of lead compounds with high binding affinity, efficient ADME characteristics, low toxicity, and high stability.

MATERIALS AND METHODS

Identification of Hits

For the Identification of Hit molecules; Million Molecules Database, Natural Product database and NCI Database available at RASPD were screened by following RASPD protocol [12]. A cut off was set at -7.0 Kcal/mol. Those molecules have successfully passed the cut off they were taken for further studies.

Filtering Hits based on Drug Likeness

Properties

Drug-likeness properties were evaluated by using Swiss ADME server [13]. To exclude molecules that are incompatible with pharmacokinetics parameters Lipinski's rule of five, Ghose rule, Veber rule, Muegge rule was applied. The molecules those have passed all these rules and having "Drug Like" properties were taken for further studies [14-17].

Lead Optimization

Docking:

To understand the molecular level interaction and get accurate poses Molecular Docking was carried out by using Auto Dock Vina implemented in AMDock [18,19]. The Crystal Structure of CHK1 was obtained from RCSB- Protein Data Bank (PDB id: 1nvq, resolution: 2.00 Å [20,21]. The crystal structure was freed from water molecules, Co-Factors, ions and covalent ligand by using the Dock-prep procedure implemented in the UCSF Chimera program [22]. Charges were computed, polar hydrogen atoms were subsequently added. As no active site was mentioned so we preferred for bind docking. The grid box centred in (X=5.062639, Y=6.464194, Z=16.857611) based on the active sites of the protein (CYS87, ALA36, LEU15, GLY16, GLU91, LEU137, GLU85, VAL23, LYS38, SER147, ASN135) [21,23]. Grid box centre points and dimensions were set to target the substrate binding-binding pocket of the protein. The best docked pose was selected based on its binding energy score and significant interactions in Active sites. Based on the ΔG, the best result was subjected to ADME and Toxicity.

ADME:

The Pharmacokinetic profile was checked by using Swiss ADME, Pre-ADMET, vnnadmet [13,24,25]. Parameters such as Solubility (LogS), Water solubility (mg/ml), Solubility Class, SKlogS buffer, Bioavailability, GI Absorption, Human Intestinal Absorption (HIA %), Madin-Darby Canine Kidney (MDCK), Caco-2 Permeability, Skin permeability (logKp) (cm/s), Partition Coefficent (LogP), Distribution Coefficient (logD), BBB (Cbrain/Cblood), BBB, Pgp Inhibition, P-gp Substrate, Plasma protein binding (%PPB), Human Liver Microsomes (HLM), CYP1A2 inhibitor, CYP3A4 inhibitor, CYP3A4 Substrate, CYP2D6 inhibitor, CYP2D6 substrate, CYP2C9 inhibitor, CYP2C19 inhibitor were selected for the studies. Those molecules have shown proper pharmacokinetic profile taken for further studies.

Toxicity:

Toxicity causes 30% of lead candidates to fail. The toxicity study was carried out by using Pre-ADMET, vnnadmet and lazar [24-26]. Toxicity parameters such Acute Oral Toxicity, Human Ether-a-Go-Related Gene Inhibition, Liver Toxicity: Cyto-toxicity, Mitochondrial Toxicity, Acute algae toxicity, AMES, Carcinogenicity (Mouse), Carcinogenicity(Rat), Carcinogenicity (Rodent), Acute daphina toxicity, hERG Blocker
Honey Bee Toxicity, Acute fish toxicity (medaka), Acute fish toxicity (minnow), Ames TA100 (-S9), Ames TA1535 (-S9), Biodegradation, MRTD (mg/day) were predicted. Only nontoxic molecules have been reported as therapeutic potential for CHK1 inhibitors.

RESULTS AND DISCUSSION

Identification of Hits

After the Screening and removing the duplicate molecule a total 3313 unique hit molecules were found that are binding with the receptor having binding affinity less than -7.0 Kcal/mol which were taken for further studies.,

Filtering Hits based on Drug Likeness Properties

To get lead like molecule Swiss ADME server was used to calculate all the hits in multiple batches. Microsoft Excel was employed for process and analysis of the data generated by Swiss ADME. Out of 3313 hit molecules only 51 Molecules Obeyed multiple drug likeness Rules such as Lipinski rule, Ghose rule, Veber rule, Muegge rule. Among them 2010 Molecules obeyed Lipinski Rule of 5 followed by 1775 molecules obeyed Veber rule, 1710 Molecules obeyed Egan rule, 1507 molecules obeyed Muegge rule, and 51 molecules obeyed Ghose rule.

Lead Optimization

Docking:

The docking was carried out to find the most suitable Confirmation of the molecule that can bind with CHK1 with lowest being energy. Out of all 51 drug like molecules, top 35 molecules were taken for further studies based on their binding energy and chemical interactions. The Molecular Docking Results of all the 53 molecules along with SMILEs and binding energy has been reported in Table 1.

ADME:

The reason behind the failure of lead molecules in the Clinical trial are low Poor ADME properties. To eliminate such molecules which having poor pharmacokinetic profile Insilco Pharmacokinetics study was conducted. Out of 35, only 17 molecules have passed all the criteria of ADME Profile. A detail view has shown in Table 2.

Tab. 1. Docking Results

Molecule Id	SMILE	Binding Energy
ZINC12132957	Cc1cc(=O)c(c2n1-c3ccccc3S[C@H](C2)c4ccccn4)C(=O)NC[C@H]5COCCO5	-10.1
ZINC20600602	c1ccc(cc1)c2c3ccccc3c(=O)n(n2)CC(=O)N[C@@H]4CCCN(C4)c5ncccn5	-10.1
ZINC12516005	Cc1cc(n(n1)c2nc3c(n2CCCc4ccccc4)c(=O)n(c(=O)n3C)CC(=O)C)C	-9
ZINC01056864	c1ccc2c(c1)CCN(C2)C(=O)c3cnn4c3nc(cc4C(F)(F)F)c5cccs5	-8.9
ZINC01056864	c1ccc2c(c1)CCN(C2)C(=O)c3cnn4c3nc(cc4C(F)(F)F)c5cccs5	-8.9
ZINC11840098	Cc1cc(n(n1)c2cccc(c2)C(=O)NC[C@H]3Cc4cc(ccc4O3)c5ccc(nn5)OC)C	-8.8
ZINC14992739	CCOC(=O)[C@@H]1CCCCN1C(=O)c2cc(cc(c2)n3cnnn3)c4cc(ccc4OC)Cl	-8.8
ZINC11784547	COc1ccc2c(c1)[nH]c(n2)CCNC(=O)CC[C@@]3(CCC(=O)N3)Cc4ccc(cc4)Cl	-8.6
ZINC00945916	Cn1c2ccccc2nc1SCC(=O)N/N=C/c3ccc(cc3)OCc4ccccc4	-8.5
ZINC12034833	CN(Cc1nc2ccccc2s1)C(=O)C[C@]3(CC(=O)N(C3=O)C4CC4)c5ccc(cc5)OC	-8.4

ZINC12447659	Cc1ccc(cc1)C2=NN(c3nc4c(n3[C@@H]2C)c(=O)n(c(=O)n4C)C)[C@@H]5CCS(=O)(=O)C5	-8.3
ZINC14885414	Cc1ccc(nc1)c2ccc3c(c2)C[C@H](O3)CNC(=O)CCN(C)[C@@H]4CCS(=O)(=O)C4	-8.3
ZINC14733310	Cc1ccc(s1)c2cc(cc(c2)S(=O)(=O)N3CCOCC3)C(=O)N(C)Cc4nccn4C	-8.3
ZINC01216760	c1ccc(cc1)C[NH+]2CCN(CC2)C(=O)c3cnn4c3nc(cc4C(F)(F)F)c5ccco5	-8.1
ZINC02859380	CCOc1ccc(cc1)NC(=O)CSc2nnc(n2C)COc3ccc4c(c3)CCCC4	-8.1
ZINC14885974	C[C@H](c1cccs1)N(C)C(=O)c2cc(cc(c2)n3cnnn3)c4cccc5c4nccc5	-8.1
ZINC19774479	c1ccc(cc1)C[NH+]2CCN(CC2)C(=O)c3cnn4c3nc(cc4C(F)(F)F)c5ccco5	-8.1
ZINC08925969	c1cc(cc(c1)Oc2ccc(cc2[N+](=O)[O-])C(F)(F)F)C(=O)N	-8
ZINC12038620	c1ccc-2c(c1)Cc3c2ccc(c3)C[NH+]4CCC[C@@H](C4)n5cc(nn5)C(=O)NCCCO	-8
ZINC00955034	CS(=O)(=O)c1ccc2c(c1)sc(n2)NC(=O)/C=C/c3ccc(cc3)OCc4ccccc4	-8
ZINC12464790	CCN(CCn1cccn1)C(=O)C[C@H]2C(=O)NCC[NH+]2Cc3ccc4ccccc4c3	-8
ZINC14530440	COc1cccc(c1)c2c3n(c([nH+]2)[C@H]4CCOC4)CCN(C3)Cc5cc6c(cc5Cl)OCO6	-8
ZINC14538250	CCn1c2c(c(n1)C(=O)N3CCOCC3)C[C@H](CC2)N4CCOc5ccc(cc5C4)Cl	-8
ZINC14740689	CN(C)C(=O)c1c2c(n(n1)Cc3ccccc3)CCN(C2)Cc4ccnc5c4cccc5	-8
ZINC12041004	Cc1ccccc1[C@@]2(CC(=O)N(C2=O)Cc3cccnc3)CC(=O)N(C)Cc4ccsc4	-8
ZINC01245157	Cc1ccc(cc1)n2c(nnc2SCC(=O)Nc3ccccc3F)c4ccncc4	-8
ZINC14987901	c1ccc(cc1)c2ccc(cc2)C[NH+]3CCC[C@H](C3)n4cc(nn4)C(=O)NCCCO	-8
ZINC02504256	c1ccc(cc1)N2CCN(CC2)C(=O)c3cnn4c3nc(cc4C(F)(F)F)c5ccco5	-8
ZINC08680620	c1ccc(cc1)C[NH+]2CCN(CC2)C(=O)c3cnn4c3nc(cc4C(F)(F)F)c5cccs5	-8
ZINC14733139	CCOC(=O)c1c2c(n(n1)Cc3ccccn3)CCN(C2)Cc4ccccc4c5ccco5	-8
ZINC12038301	CCOCCC[NH2+][C@@H]1CCc2c(sc3c2c(=O)n(cn3)C4Cc5ccccc5C4)C1	-8
ZINC14954144	CC1([C@H]2CC=C([C@@H]1C2)CN3C[C@H](C[C@H]3C(=O)OC)NC(=O)c4ccccc4n5cccn5)C	-8
ZINC12037267	COc1ccc(cc1OCc2cccs2)CN(C3CCC3)C(=O)c4cnn5c4nccc5	-8
ZINC14753959	CCN(Cc1ccncc1)[C@@H]2CCc3c(c(nn3C)C(=O)N(C)Cc4ccccc4)C2	-8
ZINC12036079	CC1(COC1)COc2cc(ccc2OC)CN(C[C@@H]3CCCO3)C(=O)c4nc5ncccn5n4	-8
ZINC12279677	Cc1ccccc1c2cnc(nc2[C@H]3CCCN(C3)C(=O)[C@@H]4CCOC4)c5ccncc5	-7.9
ZINC12300378	Cc1ccccc1C[NH+]2CCC(CC2)CN(C[C@H]3CCCO3)C(=O)c4cc(nn4C)C	-7.9
ZINC12150749	CCNC(=O)c1cn(cc(c1=O)C(=O)N2CCOc3ccc(cc3C2)Cl)Cc4ccccc4	-7.9
ZINC12278958	Cn1cc(c(=O)c2c1cccc2)C(=O)N(Cc3ccc(c(c3)OCc4ccco4)OC)C5CC5	-7.9
ZINC12450775	C[C@@H](c1cccs1)N(C)C(=O)c2cc(cc(c2)n3cnnn3)c4ccc(c(c4OC)OC)OC	-7.9
ZINC14542446	Cc1c(sc(n1)C)C(=O)N2C[C@@H](CN(C(=O)C2)Cc3cnn(c3)C)OCc4ccncc4	-7.9
ZINC14956070	CN(C)c1c(cc2cc3c(cc2n1)OCO3)CN(C[C@H]4CCCO4)C(=O)Cc5cccs5	-7.8
ZINC22077949	Cc1ccccc1n2c(nnn2)[C@H](c3ccccc3)[NH+](C)Cc4cc5c(c(c4)OC)OCO5	-7.8
ZINC14885515	Cc1ccc([nH+]c1)c2ccc3c(c2)C[C@H](O3)CNC(=O)CC[NH+](C)[C@@H]4CCS(=O)(=O)C4	-7.8
ZINC02825769	COCCCN1C(=O)c2ccc(cc2C1=O)C(=O)OCC(=O)c3ccc(cc3)c4ccccc4	-7.8
ZINC14541675	Cc1c(c(on1)C)CC(=O)N2CCc3c(c(nn3CC4CC4)C(=O)N(C)Cc5cscn5)C2	-7.7
ZINC02833795	CS(=O)(=O)CC[C@@H](C(=O)OC(c1ccccc1)c2ccccc2)N3C(=O)c4ccccc4C3=O	-7.7
ZINC00294396	CCOC(=O)[C@H]1CCC[NH+](C1)Cc2ccc(cc2)C	-7.7
ZINC14879900	Cc1csc(n1)[C@H](C)N(C)C(=O)C[C@@]2(CC(=O)N(C2=O)CCOC)c3ccccc3OC	-7.6
ZINC19853115	COCCN(Cc1cc2cc(c(cc2nc1N3CCOCC3)OC)OC)C(=O)[C@@H]4CCCO4	-7.6
ZINC20995059	Cc1cccn2c1nc(c2CN(C)C[C@@H](C)C[NH+]3CCCC3)C(=O)N4CCOCC4	-7.6

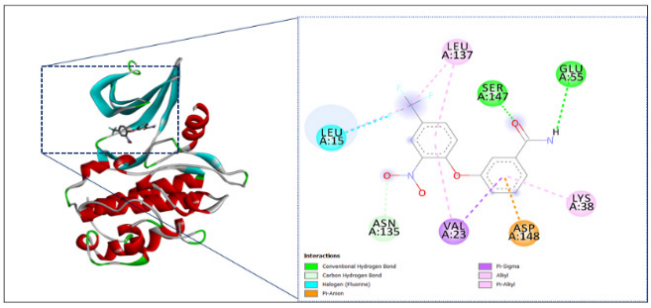

Fig. 1. CDK1-ZINC08925969 interaction depicted in Ribbon representation and 2D Depiction

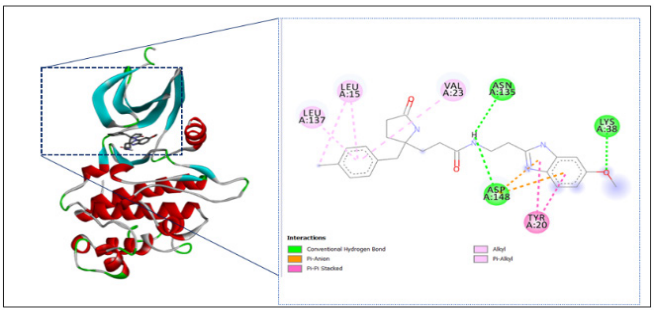

Fig. 2. CHK1- ZINC11784547 interaction depicted in Ribbon representation and 2D Depiction

Toxicity:

To be an effective drug compound, a highly biologically active lead molecule must possess low toxicity. In-silico Toxicity predictions are gaining acceptance in toxicological risk assessment. Out of 19 molecules, only 5 molecules have shown Non-Toxic properties (rows highlighted in Green) such as: Liver Toxicity: DILI, Mitochondrial Toxicity (MMP), Acute algae toxicity, AMES, Carcinogenicity (Mouse), Carcinogenicity(Rat), Carcinogenicity (Rodent), Acute daphina toxicity, in vitro hERG inhibition, Acute fish toxicity (medaka), Acute fish toxicity (minnow), Ames TA100 (+S9), Ames TA100 (-S9), Ames TA1535 (-S9). The Toxicity Prediction of the top 39 molecules listed Table 3.

Molecular Interaction Analysis:

To understand the molecular level interaction all, the top three molecules (ZINC08925969, ZINC11784547, and ZINC12516005) that have successfully passed all the Drug Likeness, ADME and Toxicity study has been taken for Molecular

Tab. 2. ADME Results

Zinc id	Solubility Class	GI Absorption	Human intestinal absorption (HIA %)	Madin-Darby Canine Kidney (MDCK)	Caco-2 Permeability	Partition Coefficent (LogP)	Distribution Coefficient (logD)	BBB (Cbrain/Cblood)	Pgp Inhibition	P-gp Substrate	Plasma protein binding [%PPB]	Human Liver Microsomes (HLM)	CYP1A2 inhibitor	CYP3A4 inhibitor	CYP3A4 Substrate
ZINC12464790	Soluble	High	92.131957	0.91684	37.1475	1.02	0.42643	No	Non	Yes	43.736916	Yes	No	No	Substrate
ZINC14885414	Soluble	High	97.30467	0.16601	9.80078	2.4	0.07455	No	Non	Yes	64.319963	Yes	No	Yes	Weakly
ZINC14538250	Soluble	High	97.428477	0.145629	50.5155	2.61	1.38984	Yes	Inhibitor	No	72.34835	Yes	No	Yes	Substrate
ZINC14733310	Soluble	High	100	0.350966	21.713	2.29	2.18163	No	Non	Yes	93.160059	Yes	No	Yes	Substrate
ZINC12036079	Soluble	High	99.446545	0.0747592	52.8658	2.22	1.5696	No	Inhibitor	Yes	69.966481	Yes	No	Yes	Substrate
ZINC12041004	Soluble	High	99.229839	3.83683	30.5199	3.11	2.74565	No	Non	Yes	91.555344	Yes	No	Yes	Substrate
ZINC01216760	Soluble	High	93.448984	0.404492	29.9402	2.27	1.53396	Yes	Inhibitor	Yes	46.438777	Yes	No	No	Substrate
ZINC19774479	Soluble	High	97.585841	0.213209	38.3199	2.27	1.8019	Yes	Inhibitor	Yes	75.010224	Yes	No	No	Weakly
ZINC12279677	Soluble	High	97.605255	2.37906	48.2635	3.41	2.82912	Yes	Non	Yes	87.991134	Yes	No	Yes	Substrate
ZINC14753959	Soluble	High	97.380853	0.896182	53.2898	3	1.67318	Yes	Inhibitor	Yes	83.909847	Yes	No	Yes	Substrate
ZINC12038620	Moderately soluble	High	89.753368	1.0062	19.2858	1.84	1.04455	No	Non	Yes	50.512485	Yes	No	No	Substrate
ZINC14987901	Moderately soluble	High	89.32498	1.89877	18.9232	1.72	1.22128	No	Non	Yes	54.274299	No	No	No	Substrate
ZINC14530440	Moderately soluble	High	97.475122	0.0586677	55.9159	3.39	3.06295	Yes	Inhibitor	Yes	84.471095	Yes	No	Yes	Substrate
ZINC14740689	Moderately soluble	High	97.669741	0.0579102	50.5699	3.2	1.98879	Yes	Inhibitor	Yes	82.007294	Yes	No	Yes	Substrate
ZINC02504256	Moderately soluble	High	97.586951	0.268624	37.2832	3.09	3.42467	Yes	Inhibitor	Yes	92.882846	Yes	No	Yes	Weakly
ZINC12447659	Moderately soluble	High	99.602877	2.13039	1.37961	1.76	2.71327	No	Inhibitor	No	100	Yes	No	No	Substrate
ZINC12516005	Moderately soluble	High	99.524021	0.0495903	24.3883	2.63	3.26059	No	Inhibitor	No	90.548132	Yes	No	Yes	Substrate
ZINC12034833	Moderately soluble	High	99.621884	0.0971435	38.3776	3.27	2.69902	No	Non	Yes	89.055638	Yes	No	Yes	Substrate
ZINC08925969	Moderately soluble	High	98.503336	0.0460023	21.3751	2.52	1.60789	No	Non	No	88.810932	Yes	Yes	Yes	Weakly
ZINC14733139	Moderately soluble	High	97.750533	0.734869	38.443	3.44	2.56431	Yes	Inhibitor	Yes	83.690586	Yes	No	Yes	Substrate
ZINC14954144	Moderately soluble	High	96.384572	0.0555437	25.3521	3.15	1.85147	Yes	Inhibitor	Yes	77.171736	Yes	No	Yes	Substrate
ZINC12132957	Moderately soluble	High	97.448023	1.47904	25.884	2.81	2.54095	No	Non	Yes	83.753715	No	No	Yes	Substrate
ZINC08680620	Moderately soluble	High	94.473155	0.190938	27.1701	2.83	1.98318	No	Non	Yes	72.27183	Yes	No	No	Substrate
ZINC20600602	Moderately soluble	High	96.70851	1.25893	24.49	2.69	2.97726	No	Non	Yes	93.709467	Yes	No	Yes	Weakly
ZINC11784547	Moderately soluble	High	91.29963	0.07203	17.3092	3.31	2.82744	No	Non	Yes	84.5226	No	Yes	Yes	Weakly
ZINC01056864	Moderately soluble	High	97.831212	0.0614135	48.0599	4.13	3.8651	No	Inhibitor	Yes	93.822916	Yes	Yes	Yes	Weakly
ZINC11840098	Moderately soluble	High	97.831212	0.0614135	48.0599	3.64	3.8651	No	Inhibitor	Yes	93.822916	Yes	No	Yes	Weakly
ZINC12037267	Moderately soluble	High	98.650061	0.0901468	54.503	3.91	4.08286	No	Inhibitor	Yes	93.073048	No	No	Yes	Substrate
ZINC12038301	Moderately soluble	High	94.346549	7.3874	23.5531	3.2	1.47678	No	Non	Yes	36.813913	Yes	No	Yes	Substrate
ZINC01245157	Moderately soluble	High	96.772975	0.0985069	44.7343	3.7	4.7439	No	Inhibitor	No	99.446876	No	Yes	Yes	Weakly
ZINC14992739	Moderately soluble	High	99.578491	0.0614725	22.5019	3.52	3.82613	No	Inhibitor	No	90.591818	Yes	Yes	Yes	Substrate
ZINC14885974	Poorly soluble	High	98.571171	0.457832	37.013	3.92	4.2395	No	Inhibitor	Yes	92.200846	Yes	No	Yes	Substrate
ZINC02859380	Poorly soluble	High	97.179052	20.0541	51.9786	3.92	5.40364	No	Inhibitor	No	96.692417	No	No	Yes	Substrate
ZINC00945916	Poorly soluble	High	96.871525	0.86525	45.2023	4.07	5.64578	No	Inhibitor	No	96.895471	Yes	Yes	Yes	Substrate
ZINC00955034	Poorly soluble	Low	97.149361	0.241538	19.746	4.33	4.69202	No	Inhibitor	No	100	Yes	No	Yes	Weakly

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Tab. 3. Toxicity Results

ZINC ID	Acute Oral Toxicity	Human Ether-a-go-go-Related Gene Inhibition	Liver Toxicity: Cyto- toxicity	Mitochondrial Toxicity (MMP)	AMES	Carcinogenic-ity (Mouse)	Carcinoge-nicity(Rat)	Carcinogenicity (Rodent)	hERG Blocker	Honey bee Toxicity	Ames TA100 (+S9)	Ames TA100 (-S9)	Ames TA1535 (-S9)
ZINC01056864	III	Weak inhibitor	No	No	No	positive	negative	non-carcinogenic	Yes	Low HBT	positive	negative	negative
ZINC12037267	III	Weak inhibitor	No	No	No	negative	negative	carcinogenic	No	Low HBT	positive	negative	negative
ZINC14733310	III	Weak inhibitor	No	No	Yes	negative	negative	non-carcinogenic	Yes	Low HBT	positive	negative	negative
ZINC12034833	III	Strong inhibitor	No	No	No	negative	negative	non-carcinogenic	Yes	Low HBT	negative	negative	negative
ZINC14992739	III	Weak inhibitor	No	No	No	negative	negative	non-carcinogenic	Yes	Low HBT	positive	negative	negative
ZINC12516005	III	Weak inhibitor	No	No	No	negative	negative	non-carcinogenic	No	Low HBT	negative	negative	negative
ZINC12036079	III	Weak inhibitor	No	No	Yes	negative	positive	carcinogenic	Yes	Low HBT	positive	positive	negative
ZINC12041004	III	Weak inhibitor	No	No	No	negative	negative	non-carcinogenic	Yes	Low HBT	positive	negative	negative
ZINC08925969	III	Weak inhibitor	Yes	Yes	No	negative	negative	non-carcinogenic	No	Low HBT	negative	negative	negative
ZINC11840098	III	Weak inhibitor	No	No	Yes	negative	positive	non-carcinogenic	Yes	Low HBT	negative	negative	negative
ZINC12132957	III	Weak inhibitor	No	No	No	negative	negative	non-carcinogenic	Yes	Low HBT	positive	positive	negative
ZINC14885414	III	Weak inhibitor	No	No	Yes	negative	negative	non-carcinogenic	Yes	Low HBT	negative	negative	negative
ZINC01245157	III	Weak inhibitor	No	No	No	negative	positive	carcinogenic	No	Low HBT	negative	negative	negative
ZINC20600602	III	Strong inhibitor	No	No	No	negative	negative	non-carcinogenic	Yes	Low HBT	positive	negative	negative
ZINC08680620	III	Weak inhibitor	No	No	No	negative	positive	non-carcinogenic	Yes	Low HBT	positive	negative	negative
ZINC12038301	III	Weak inhibitor	No	No	No	negative	negative	carcinogenic	Yes	Low HBT	negative	positive	negative
ZINC11784547	III	Weak inhibitor	No	No	No	negative	negative	non-carcinogenic	No	Low HBT	negative	negative	negative

Interaction Analysis. All the molecules have been found that they are effectively binding with the same amino acids present in the active site of CHK1 (CYS87, ALA36, LEU15, GLY16, GLU91, LEU137, GLU85, VAL23, LYS38, SER147, ASN135) and they have formed sufficient Hydrogen bonds to make complex. The interaction details of CHK1 all the molecules have been reported in ribbon representation and 2D Depiction in Figure 1-3.

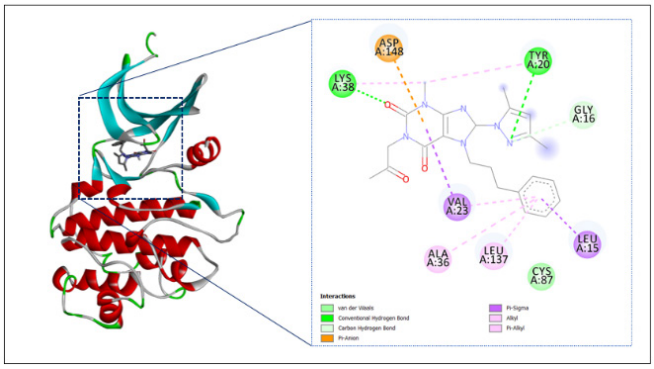

Fig. 3. CHK1- ZINC12516005 interaction depicted in Ribbon representation and 2D Depiction

CONCLUSION

The identified molecules ZINC08925969, ZINC11784547, ZINC11972241, and ZINC12516005 exhibit drug-like properties, ADME, and non-toxicity with strong binding energy at the active site of CHK1 and interacting Key amino acid residues with stable hydrogen bonds and a thermodynamically favourable receptor-ligand interaction. Therefore, we wish to report that these compounds may be effective CHK1 inhibitors.

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DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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