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ORIGINAL ARTICLE / ÖZGÜN MAKALE

TARGETTING THE 3BGQ - PIM1 KINASE INTERACTION WITH A SERIES OF NOVEL DITHIOCARBAMATE SUBSTITUTED 2-OXOINDOLE DERIVATIVES - *IN SILICO* STUDIES

3BGQ - PIM1 KİNAZ ETKİLEŞİMİNİ HEDEF ALAN YENİ DİTİYOKARBAMAT İLE SÜBSTİTÜE 2-OKSOİNDOL TÜREVLERİNİN İN SİLİKO ÇALIŞMALARI

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ABSTRACT

Objective: *Cancer is the major cause of mortality in most of the developing countries. Enormous chemotherapeutic agents developed are still need improvements in survival rates and quality of life for cancer patients. Pro-viral Integration site of Moloney murine leukemia virus (PIM1) is a family of serine/threonine kinase, regulated by calcium/calmudulin have been identified as a unique molecular target in oncogenesis. PIM1 has significant role in cell cycle regulation, cell survival, apoptosis, cellular senescence, drug resistance and it is emerging as a potential biomarker in number of human malignancies. Today many interesting PIM1 inhibitors are developed and few withdrawn from phase1 and 2 clinical trials, due to lack of bioavailability and toxicity. Hence the purpose of the present study is to develop more potent and less toxic compounds.*

Material and Method: *A series of novel 2-oxindoles with dithiocarbamates were designed as PIM1 inhibitors. All molecules were subjected to Molsoft, Molinspiration, Swiss ADME and pkCSM to predict their molecular properties which are important for drug candidate. Further, in order to find the binding affinity of designed molecules with PIM1 kinase protein and to rationalize their anticancer activity, molecular docking study was performed.*

Result and Discussion: *Results revealed that all designed compounds fulfilled the criteria for good oral bioavailability, low toxicity and the potential inhibitory activities. All of them were docked into active site of*

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*PIM1 kinase with AutoDock Vina software. In conclusion, according to the binding energy values, compound 16 and 24 showed equivalent dock score -9.7 kcal/mol which are comparable with previously reported compounds **AZ1208 and SGI 1776**. This finding will help the researchers in the design of a better drug for the treatment of cancer.*

Keywords: *AutoDock Vina, dithiocarbamate, PIM1 Kinase, QSAR, 2-oxindole*

ÖZ

Amaç: *Kanser, gelişmekte olan ülkelerin çoğunda başlıca ölüm nedenidir. Geliştirilen muazzam kemoterapötik ajanların, kanser hastalarının hayatta kalma oranları ve yaşam kaliteleri açısından hala iyileştirilmeleri gerekmektedir. Moloney murin lösemi virüsünün (PIM1) pro-viral entegrasyon bölgesi, kalsiyum/kalmudulin tarafından düzenlenen bir serin/treonin kinaz ailesidir, onkogenezde benzersiz bir moleküler hedef olarak tanımlanmıştır. PIM1 hücre döngüsü düzenlenmesi, hücre sağkalımı, apoptozu, hücresel yaşlanması ve ilaç direncinde önemli bir role sahiptir ve insan malignitelerinin sayısında potansiyel bir biyobelirteç olarak ortaya çıkmaktadır. Bugün birçok ilginç PIM1 inhibitörü geliştirildi ve biyoyararlanım ve toksisite eksikliği nedeniyle birkaçı faz 1 ve 2 klinik çalışmalardan çekildi. Dolayısıyla bu çalışmanın amacı, daha güçlü ve daha az toksik bileşikler geliştirmektir.*

Gereç ve Yöntem: *Ditiyokarbamat içeren bir seri yeni 2-oksindoller PIM1 inhibitörü olarak tasarlandı. Tüm moleküllerin ilaç adayı için önemli olan moleküler özelliklerini tahmin etmek için Molsoft, Molinspiration, Swiss ADME ve pkCSM programları kullanıldı. Ayrıca, tasarlanan bileşiklerin PIM1 kinaz proteini ile bağlanma afinitelerini bulmak ve antikanser aktivitelerini rasyonalize etmek için, moleküler yerleştirme çalışması yapıldı.*

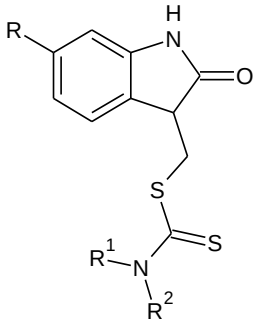
Sonuç ve Tartışma: *Sonuçlar, tasarlanan tüm bileşiklerin iyi oral biyoyararlanım, düşük toksisite ve potansiyel inhibitör aktiviteler için kriterleri karşıladığını ortaya koymaktadır. Tüm bileşiklerin PIM1 kinazın aktif bölgesine yerleştirilmesi Auto DockVina yazılımı ile gerçekleştirildi. Sonuç olarak, bağlanma enerjisi değerlerine göre, bileşik 16 ve 24 daha önce bildirilen AZ1208 ve SGI 1776 bileşikleri ile karşılaştırılabilir eşdeğer dock skoru -9.7 Kcal/mol gösterdi. Bu bulgu, araştırmacılara kanser tedavisi için daha iyi bir ilacın tasarımında yardımcı olacaktır.*

Anahtar Kelimeler: *AutoDock Vina, ditiyokarbamat, PIM1 Kinaz, QSAR, 2-oksoindol*

INTRODUCTION

Pro-viral Integration site of Moloney murine leukemia virus (PIM) are a family of serine/threonine kinases of calcium/calmodulin-dependent [1]. PIM kinases include three genes-PIM1, PIM2 and PIM3. They are involved in multiple human cancers including prostate cancer, acute myeloid leukemia, and other hematopoietic malignancies. PIM 1 kinases are unique and divergent from other kinases with greater than 60% parity amongst each member [2]. PIM 1 kinase play an important role in multiple cellular functions which include cell cycle regulation, cell survival, apoptosis, cellular senescence, and drug resistance [3]. The inhibitors which inhibit or slow the chemical action of PIM 1 kinases include flavonoids, cinnamic acids, Isoxazoloquinoline-3,4diones, benzoisoxazoles, imidazole (1,2-b) pyridazines, most of them are in clinical trials [4]. Although these compounds have exhibited good potency and minimal toxicities *in vitro* cell lines, their clear toxicity analysis is still being undertaken by researchers worldwide and there is wide scope to develop new leads. Other side, oxindole has emerged as a valuable scaffold in medicinal chemistry possessing diverse range of pharmacological activities [5]. The synthetic oxindole derivatives Sunitinib is marketed anti-cancer agent for gastrointestinal stromal tumors and metastatic renal cell cancer [6]. Further optimization of the

substituents around the oxindole nucleus resulted in several oxindole based kinase inhibitors that are in clinical trials SU11248, SU5416, SU5614, SU6668, SU14813 and SU4984 [7]. In view of the literature, we designed a novel 2-oxoindole with substitution of dithiocarbamate at 3rd and electron releasing or elctron donating groups at sixth position as shown in fig. 1. Molecular docking can strongly support and help the design of novel, more potent inhibitors by revealing the mechanism of drug-receptor interaction.



R = NO_2/ CH_3

NR^1R^2 = Alkyl/Cycloalkyl /Aralkyl

Figure 1. General structure of designed 2-oxoindole derivatives as PIM1 inhibitors.

Table 1. Structures and IUPAC names of the designed oxindole derivatives

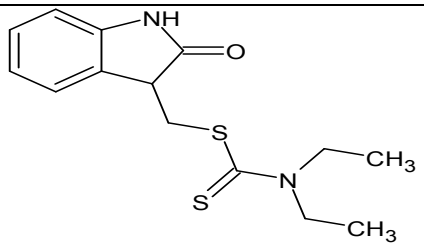
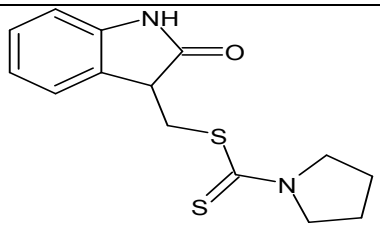
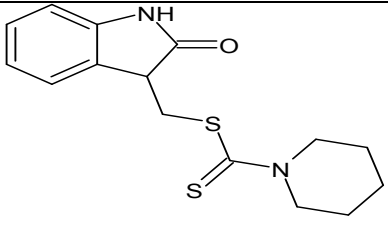
Compound Code	Compound Structure	Chemical Name
1.		(2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl diethylcarbamodithioate
2.		(2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl pyrrolidine-1-carbodithioate
3.		(2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl piperidine-1-carbodithioate

Table 1 (*continued*). Structures and IUPAC names of the designed oxindole derivatives.

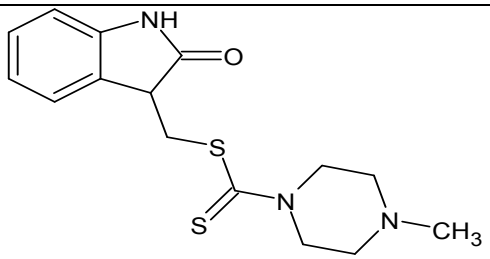
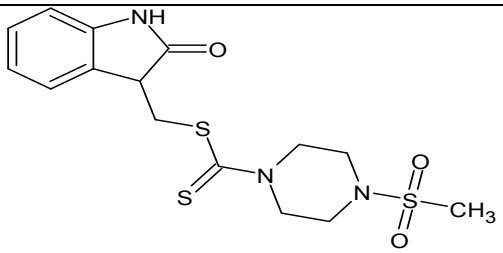
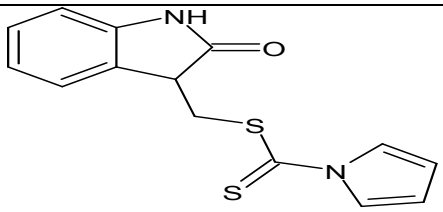
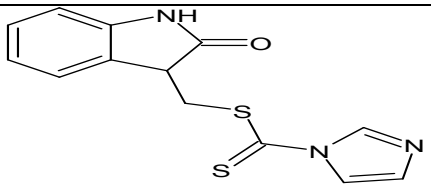
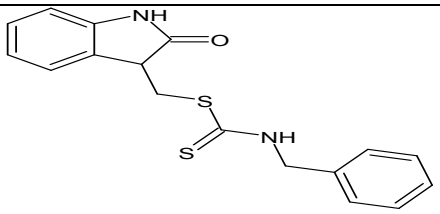
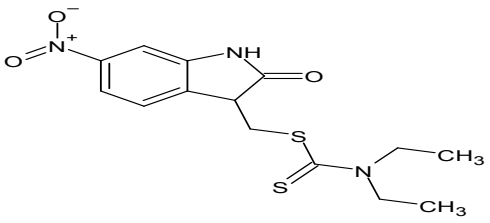
4.		(2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 4-methylpiperazine-1-carbodithioate
5.		(2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 4-(methanesulfonyl)piperazine-1-carbodithioate
6.		(2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 1*H*-pyrrole-1-carbodithioate
7.		(2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 1*H*-imidazole-1-carbodithioate
8.		(2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl benzylcarbamodithioate
9.		(5-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl diethylcarbamodithioate

Table 1 (*continued*). Structures and IUPAC names of the designed oxindole derivatives

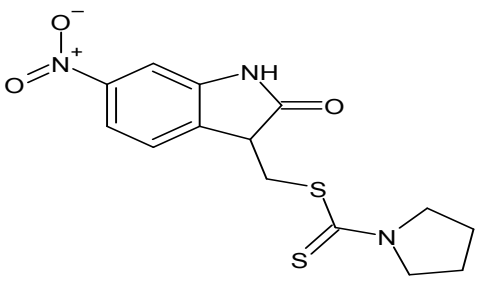
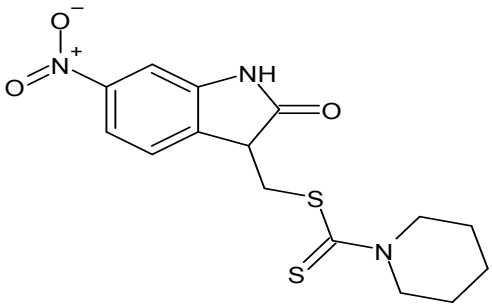
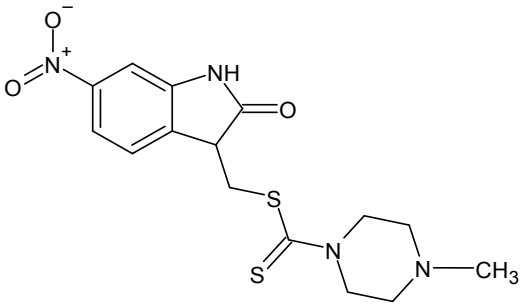
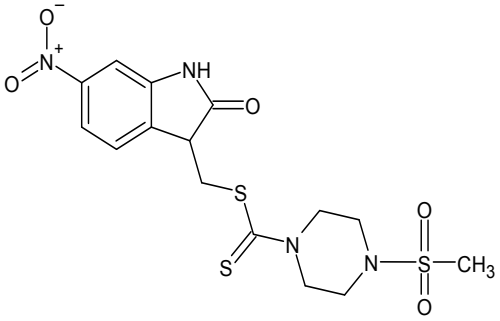
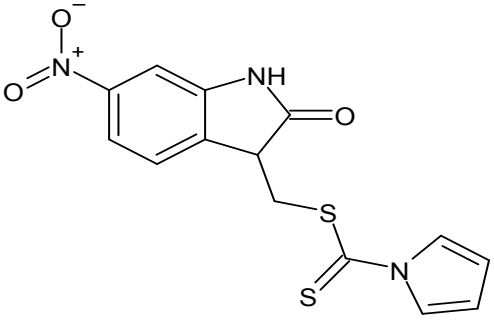
10.		(5-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl pyrrolidine-1-carbodithioate
11.		(5-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl piperidine-1-carbodithioate
12.		(5-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 4-methylpiperazine-1-carbodithioate
13.		(5-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 4-(methanesulfonyl)piperazine-1-carbodithioate
14.		(5-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 1*H*-pyrrole-1-carbodithioate

Table 1 (*continued*). Structures and IUPAC names of the designed oxindole derivatives

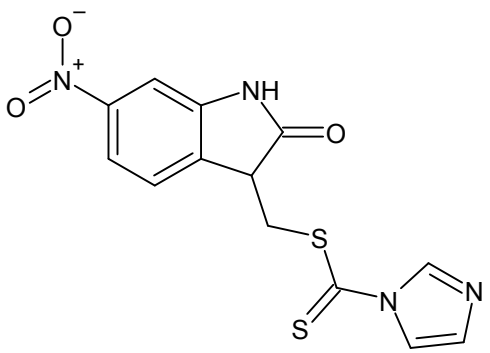
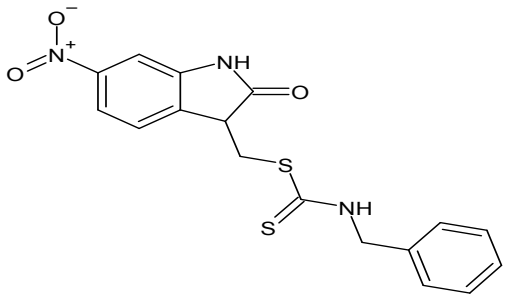
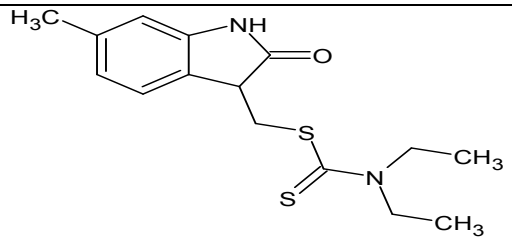
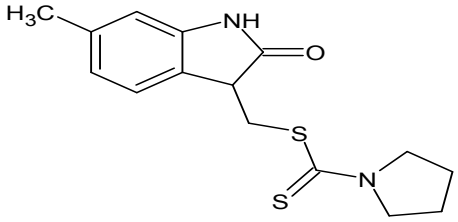
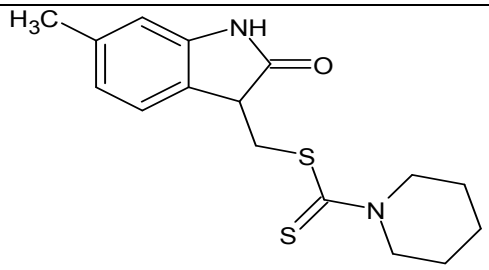
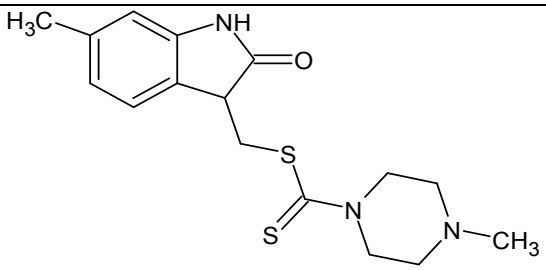
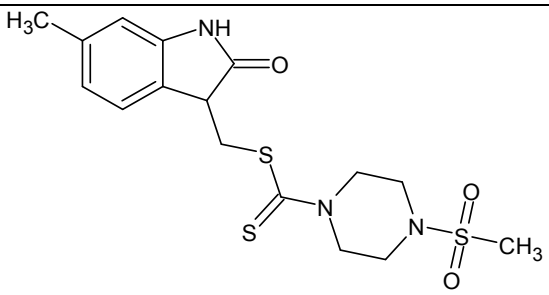
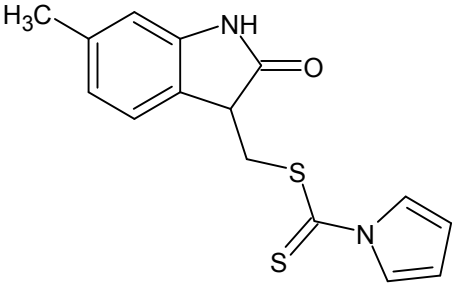
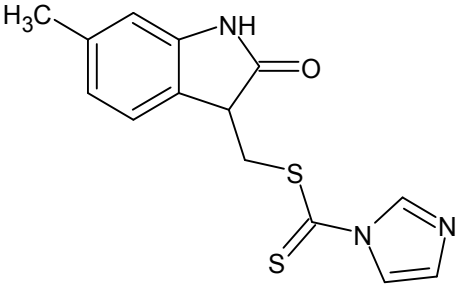
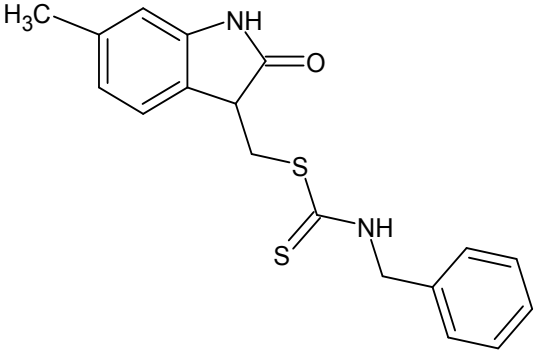
15.		(5-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 1*H*-imidazole-1-carbodithioate
16.		(5-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl benzylcarbamodithioate
17.		(5-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl diethylcarbamodithioate
18.		(5-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl pyrrolidine-1-carbodithioate
19.		(5-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl piperidine-1-carbodithioate

Table 1 (*continued*). Structures and IUPAC names of the designed oxindole derivatives

20.		(5-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 4-methylpiperazine-1-carbodithioate
21.		(5-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 4-(methanesulfonyl)piperazine-1-carbodithioate
22.		(5-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 1*H*-pyrrole-1-carbodithioate
23.		(5-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl 1*H*-imidazole-1-carbodithioate
24.		(5-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl benzylcarbamodithioate

MATERIAL AND METHOD

Molecular Descriptors, Bioactivity Prediction and ADMET Properties

In the drug discovery process, computational (*in silico*) enables optimization of lead molecules by comparing absorption, distribution, metabolism, excretion and toxicity (ADMET) properties and screening of molecules [8]. Data sets of 24 molecules have been chosen for this study. The softwares used are SwissADME (Free, CC-BY 4.0 Creative Commons 4.0 International License, Swiss Institute of Bioinformatics, Switzerland), Molsoft (Free, Molsoft LLC, US), Molinspiration Cheminformatics free web services (Slovensky Grob, Slovakia), pkCSM (Free, Bio 21 Institute University of Melbourne, 30 Flemington Rd Parkville, Melbourne, Australia). The molecules were subjected to Swiss ADME; a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. This server is useful in the prediction of properties like number of hydrogen bond donor, number of hydrogen bond acceptor, molar refractivity, total polar surface area (TPSA), Lipinski violation [9]. Molsoft; a leading provider of tools, databases and consulting services in the area of structure prediction, structural proteomics, bioinformatics, cheminformatics, molecular visualization and animation and rational drug design. From this server, lop P (o/w) values are predicted [10]. Molinspiration; offers broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SD file conversion, normalization of molecules, generation of tautomer's, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction. This software is used to predict GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor, enzyme inhibitor [11]. pkCSM (Free, Bio 21 Institute University of Melbourne, 30 Flemington Rd Parkville, Melbourne, Australia); a novel method for predicting and optimizing small molecule pharmacokinetic and toxicity properties which relies on distance-based graph signatures. It predicts their pharmacokinetic (absorption, distribution, metabolism, excretion) and toxicity (ADMET) properties. It helps in the prediction of human intestinal absorption (HIA%), *in vitro* skin permeability, *in vitro* VDss (human), *in vitro* blood brain barrier permeability and toxicity [12].

Molecular Docking Studies

The molecular modelling-based approach was adopted to understand the structure of the PIM1 protein along with binding efficiency of various ligand molecules considered for this study. The three-dimensional (3D) structure of PIM1 kinase (PDB ID: 3BGQ) was downloaded from Brook heaven Protein Data Bank and saved as a Brookhaven protein data bank file [16]. The 2D structures of ligands were generated from the ACD/Chemsketch Software. The generated ligands cleaned and performed 3D optimization then saved in the MDL Molfile format. The ligands were then converted to a PDB file

format using the Open Babel chemistry toolbox. AutoDock Vina [18] (Academic version.1.2.0, Molecular Graphics Lab (now CCSB) at The Scripps Research Institute) was used for molecular docking studies. A grid was generated around the co-crystallized ligand. The co-ordinates (x = -8.298, y = 40.748, z = 0.228) were generated with the help of MGL Tools and Pharmit: interactive exploration of chemical space [17]. Prepared pdbqt files for both target and ligands. Created in house batch file of ligands and target and docking performed in the absence of water molecules for all 26 molecules (24 + 2 standard molecules) [19]. The molecules were analyzsed after docking and visualized in the discovery studio for the interactions with the active site amino acids [13].

RESULT AND DISCUSSION

Molecular Properties

The molecular properties of the designed compounds **1-24** were predicted shown in Table 2. It is observed that all the compounds have significant HIA capacity as the value ranges from 78.59 to 93.80. And compounds are less permeable to Caco-2 cells with the range of values between 0.69-1.54 cm/sec. The *in vivo* blood brain barrier penetration values are ranged from -0.773 to 0.386 confirming them as CNS inactive compounds. The toxicity evaluation revealed that all the compounds are non-toxic in terms of mutagenicity, tumorigenicity, irritancy, hepatotoxicity and reproductive toxicity. Additionally, we have compared the above properties of designed compounds with reported PIM 1 Kinase inhibitors, SGI 1776 and AZ 1208. This over all evaluation has proved that the compounds are safer to the normal cells and suitable anti-tumor agents.

The bioactivity parameters of compounds **1-24** (Table 3) like G Protein-coupled Receptor (GPCR) Ligand property, ion channel modulator, kinase inhibitor, nuclear receptor ligand interactions, protease inhibitor and enzyme inhibitor were predicted for the designed compounds and compared with the values of SGI 1776 and AZ 1208. The results support them as safer compounds with good binding capacities and cell growth inhibitors.

The predicted Lipinski properties of **1-24** (Table 4) with valid scorings bolster and their safer drug behaviour. An orally available drug is elected to be in agreement with Lipinski's rule if the molecular weight is less than 500 Daltons, the number of hydrogen bond donors is less than 5, the number of hydrogen bond acceptors is less than 10, the partition co-efficient (log P) value is less than 5 and the molecular refractivity is within the range. The results exhibit that compounds stratify to Lipinski's, so they should theoretically manifest good oral absorption. The total polar surface area was calculated and is observed that the value is less than 140 for most of the compounds. This acceptability with respect to Lipinski rule proves them as safe administrable drugs and establishes their pharmacological activity [14 and 15].

Table 2. Predicted molecular properties of the designed oxindole derivatives

Compd code	Human intestinal absorption (HIA, %)[a]	*In Vitro* Caco-2 Cell Permeability (log Papp in 10-6cm/s)[b]	*In Vitro* skin Permeability (log Kp)[c]	*In vitro* VDss (human) (log L/kg)[d]	*In vitro* blood-brain barrier permeability (log BB)[e]	Toxicity
1.	90.692	1.376	-3.184	0.254	0.225	Non toxic
2.	90.527	1.545	-2.67	0.354	0.269	Non toxic
3.	90.138	1.548	-2.688	0.384	0.282	Non toxic
4.	91.836	1.364	-3.376	0.762	0.203	Non toxic
5.	86.373	0.691	-3.049	-0.136	-0.616	Non toxic
6.	91.997	1.74	-2.607	0.066	0.356	Non toxic
7.	93.366	0.91	-2.735	-0.027	0.386	Non toxic
8.	92.187	1.49	-3.098	0.477	0.222	Non toxic
9.	88.313	0.881	-2.801	0.135	-0.328	Non-toxic
10.	90.393	0.853	-2.799	0.209	-0.168	Non-toxic
11.	90.005	0.854	-2.799	0.237	-0.146	Non-toxic
12.	89.457	0.901	-2.839	0.644	-0.688	Non-toxic
13.	78.59	1.014	-2.799	-0.141	-0.773	Non-toxic
14.	89.984	0.88	-2.769	-0.026	-0.465	Non-toxic
15.	89.554	0.897	-2.735	0.596	-0.919	Non-toxic
16.	88.446	0.9	-2.766	0.126	-0.358	Non-toxic
17.	90.531	1.216	-3.178	0.288	0.189	Non-toxic
18.	91.797	1.238	-2.983	0.493	0.259	Non-toxic
19.	91.408	1.241	-2.978	0.526	0.272	Non-toxic
20.	91.674	1.204	-3.366	0.784	0.168	Non-toxic
21.	93.802	0.58	-3.62	-0.035	-0.734	Non-toxic
22.	93.183	1.393	-2.628	0.173	0.334	Non-toxic
23.	92.636	1.267	-2.749	0.383	0.075	Non-toxic
24.	89.356	1.436	-2.928	0.303	0.28	Non-toxic
SGI 1776	96.08	24.30	-2.735	0.662	1.18	Mutagenicity
AZ 1208	96.02	3.11	-2.699	1.168	0.82	Mutagenicity

a. Human intestinal absorption is the sum of bioavailability and absorption values evaluated from the ratio of cumulative excretion in urine, bile and feces; **b**. Caco-2 cells are derived from human colon adenocarcinoma and posses multiple drug transport pathways through the intestinal epithelium; **c**. skin permeability is a significant consideration for many consumer product efficacy, and of interest for the development of transdermal drug delivery; **d**. the steady state volume of distribution (vdss) is the theoretical volume that the total dose of a drug would need to be uniformly distributed to give the same concentration as in blood plasma;**e**. the ability of a drug to cross into the brain is an important parameter to consider to help reduce side effects and toxicities or to improve the efficiency of drugs whose pharmacological activity is within the brain.

Collectively and based on the estimated ligand efficiency, drug likeliness and pharmacokinetic predictors, the designed compounds considered as a pharmacologically active, which can be considered on progressing further potential hits.

Table 3. *In silico* predicted bioactivity properties of the designed oxindole derivatives

Compound code	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1.	-0.42	-0.86	-0.87	-0.92	-0.94	-0.28
2.	-0.34	-0.76	-0.79	-0.83	-0.78	-0.33
3.	-0.28	-0.75	-0.75	-0.78	-0.75	-0.19
4.	-0.24	-0.70	-0.59	-0.77	-0.71	-0.20
5.	-0.20	-0.87	-0.61	-0.69	-0.39	-0.21
6.	-0.21	-0.25	-0.19	-0.26	-0.52	0.00
7.	-0.15	-0.19	-0.06	-0.41	-0.45	0.21
8.	-0.23	-0.56	-0.48	-0.51	-0.47	-0.14
9.	-0.45	-0.81	-0.82	-0.78	-0.86	-0.36
10.	-0.38	-0.72	-0.75	-0.71	-0.72	-0.40
11.	-0.35	-0.71	-0.74	-0.70	-0.71	-0.29
12.	-0.33	-0.67	-0.63	-0.72	-0.70	-0.30
13.	-0.33	-0.82	-0.68	-0.70	-0.47	-0.29
14.	-0.27	-0.28	-0.24	-0.23	-0.50	-0.12
15.	-0.22	-0.23	-0.12	-0.36	-0.43	0.06
16.	-0.34	-0.55	-0.56	-0.53	-0.51	-0.25
17.	-0.40	-0.91	-0.83	-0.84	-0.91	-0.32
18.	-0.32	-0.82	-0.76	-0.76	-0.76	-0.38
19.	-0.28	-0.81	-0.73	-0.72	-0.73	-0.25
20.	-0.24	-0.75	-0.58	-0.72	-0.70	-0.26
21.	-0.23	-0.91	-0.63	-0.67	-0.41	-0.26
22.	-0.21	-0.33	-0.19	-0.22	-0.51	-0.06
23.	-0.15	-0.28	-0.06	-0.36	-0.44	0.14
24.	-0.24	-0.62	0.49	-0.49	0.48	-0.20
SGI 1776	-0.2	-0.27	-0.13	-0.2	-0.19	-0.21
AZ 1208	-1.26	-1.22	-0.75	-1.01	-1.33	-0.46

Abbreviations: GPCRL: G protein-coupled receptor Ligand; ICM: Ion channel modulator; KI: Kinase inhibitor; NRL: Nuclear receptor ligand; PI: Protease inhibitor; EI: Enzyme inhibitor. For organic compounds, If the bioactivity score is (>0), then it is active, if (-5.0-0.0) then moderately active, if (<-5.0) then inactive.

Table 4. *In silico* predicted lipinski's properties of the designed oxindole derivatives

Compound code	M.W. g/mol	H.B. Don.	H.B. Acc.	Log P (o/w)	M.R. cm^3/mol	TPSA $Å^2$	Lip. Vio.
1.	294.44	1	1	2.87	88.85	89.73	0
2.	292.42	1	1	2.78	90.66	89.73	0
3.	306.45	1	1	3.06	95.46	89.73	0
4.	321.46	1	2	1.87	102.27	92.97	0
5.	385.52	1	4	1.43	111.24	135.49	0
6.	288.39	1	1	2.99	85.50	91.42	0
7.	289.38	1	2	1.61	83.30	104.31	0
8.	328.45	2	1	2.65	98.83	98.52	0
9.	339.43	1	3	1.88	97.68	135.55	0
10.	337.42	1	3	1.79	99.48	135.55	0
11.	351.44	1	3	2.08	104.28	135.55	0
12.	366.46	1	4	0.88	111.10	138.79	0
13.	429.53	1	5	0.44	118.06	178.07	0
14.	333.39	1	3	2.00	94.33	137.24	0
15.	334.37	1	4	0.63	92.12	150.13	0

Table 4 (*continued*). *In silico* predicted lipinski's properties of the designed oxindole derivatives

16.	373.45	2	3	2.63	107.65	144.34	0
17.	308.46	1	1	3.32	93.82	89.73	0
18.	306.45	1	1	3.23	95.62	89.73	0
19.	320.47	1	1	3.52	100.43	89.73	0
20.	335.49	1	2	2.32	107.24	92.97	0
21.	399.55	1	4	1.88	116.20	135.49	0
22.	302.41	1	1	3.44	90.47	91.42	0
23.	303.40	1	2	2.07	88.26	104.31	0
24.	342.48	2	1	3.10	103.79	98.52	0
SGI 1776	405.42	1	7	4.27	107.95	54.68	0
AZ 1208	221.28	1	2	2.42	65.26	71.47	0

Molecular Docking

The designed compounds were docked against the human PIM1 (PDB ID: 3BGQ) to predict their binding mode. The compounds were found to have binding energies in the range of -7.20 to -9.70 kcal/mol were illustrated in Table 5. They formed 1–3 hydrogen bonds with LEU 44, LYS 67, GLU 121 and ASP 186 amino acids in the active site. In addition, different hydrophobic interactions were also observed including pi-sigma, pi-pi staked, pi-alkyl, and alkyl types with LEU 174, ILE 185, LEU 120, ALA 65, ARG 122 and PHE 49 are shown in Figure 2. Among the series, compound 16 and compound 24 are showed equivalent dock score values (-9.7 kcal/mol) which are comparable to reference compounds AZD1208 and SGI1776. Overall results demonstrating, dithiocarbamate with aromatic ring as a side chain at third position and electron with drawing (nitro) or electron releasing (methyl) on oxindole ring important for PIM1 Kinase inhibition activity.

Table 5. Binding energies and interactions between human PIM1 (PDB ID: 3BGQ) and designed oxindole derivatives

Ligand	Hydrogen bond Interactions	Hydrophobic Interaction	Dock score values (kcal/mol)
1.	NIL	ILE:104, ALA:65	-7.2
2.	GLU:121, GLU:171.	LEU:120, ILE:104, PHE:49, ILE:185, ALA:65, ILE:104, LEU-120, PHE:49, ILE:185, ARG:122, LEU:174, ASP:128, GLU:171, ASN:172, VAL:52, ASP:186, LYS:67	-8.1
3.	GLU:121	No Interactions	-8.4
4.	GLU:121, GLU:171, ASN:172	LYS:67, ILE:104, LEU:120, ILE:185, PHE:49, ILE:104, LYS:67, LEU:120, ILE:185, ASP:128, LEU:4 4, PRO:123, LEU:174, VAL:52, ARG:122, ALA:65, PHE:49, ASN:172, ASP:186, GLU: 89	-7.9
5.	GLU:121, GLU:171.	No Interactions	-8.1
6.	GLU:171	VAL:52, ILE:104, LEU:120, ALA:65, ILE:185	-7.8

Table 5 (*continued*). Binding energies and interactions between human PIM1 (PDB ID: 3BGQ) and designed oxindole derivatives

7.	LYS:67, ASP18	LEU:120, ILE:104, VAL:52, LEU:174, ALA:65, ILE:185	-7.5
8.	GLU:121	ILE:104, LEU:120, ALA:65, ILE:185	-9
9.	GLU:121, LYS:67, ASP:186	ALA:65, LEU:120, ILE:185, PHE:49, VAL:52, ILE:104	-7.9
10.	GLU:121, LYS:67, ASP:186	ILE:185, VAL:52, LEU:120, ALA:65, PHE:49, ILE:104	-8.6
11.	ASP:186, LYS:67	ALA:65, ILE:185, VAL:52, PHE:49, LEU:120, ILE:104	-9.1
12.	GLU:121, LYS:67 ASN:172, ASP:186	ILE:104, ILE:185, PHE:49, ALA:65, LEU:120, VAL:52	-8.7
13.	ASP:186, GLU:121, LYS:67	LEU:120, ILE:185, ILE:104, ALA:65, VAL:52	-8.7
14.	GLU:121, LYS:67, ASP:186	LEU:120, ILE:104, ALA:65, VAL:52, ILE:185	-8.4
15.	GLU:121, ASP:186, LYS:67	ILE:104, LEU:120, ILE:185, ALA:65, VAL:52	-7.9
16.	GLU:121, LYS:67, ASP:18, GLU:121.	ILE:185, ALA:65, VAL:52, ILE:104, LEU:120	-9.7
17.	GLU:121	VAL:52, ILE:104, LEU:120, ALA:65 PHE:49, ILE:185	-7.6
18.	GLU:121, GLU:171	PHE:49, ILE:104, VAL:52, ALA:65, LEU:120, ILE:185	-8.6
19.	GLU:121	PHE:49, ILE:104, ILE:185, VAL:52, ALA:65, LEU:120	-9
20.	ASP:186, GLU:121, GLU:171, ASN:172,	ILE:104, ILE:185, PHE:49, LEU:120, ALA:65, VAL:52	-8.6
21.	GLU:121, GLU:171	ILE:104, ILE:185, LEU:120, VAL:52, ALA:65	-8.7
22.	GLU:121, GLU:171	VAL:52, ALA:65, ILE:104, LEU:120, ILE:185	-8.6
23.	GLU:121, GLU:171	ILE:104, ALA:65, LEU:120, ILE:185	-8.2
24.	GLU:121	ALA:65, LEU:120, ILE:104, VAL:52, ILE:185	-9.7
SGI-1776	LYS:67, GLU:121, ASP:128, GLU:171	ILE:185, ILE:104, LEU:120, ALA:65, VAL:52, PHE:49, LEU:44, ARG:122, LEU:174, ILE:185, LEU:120.	-10.1
AZD-1208	LEU:44	VAL:52, ALA:65, ARG:122, LEU:174, VAL:126, LEU:44, LEU:174, LEU:120, ILE:185, LYS:67	-9.7

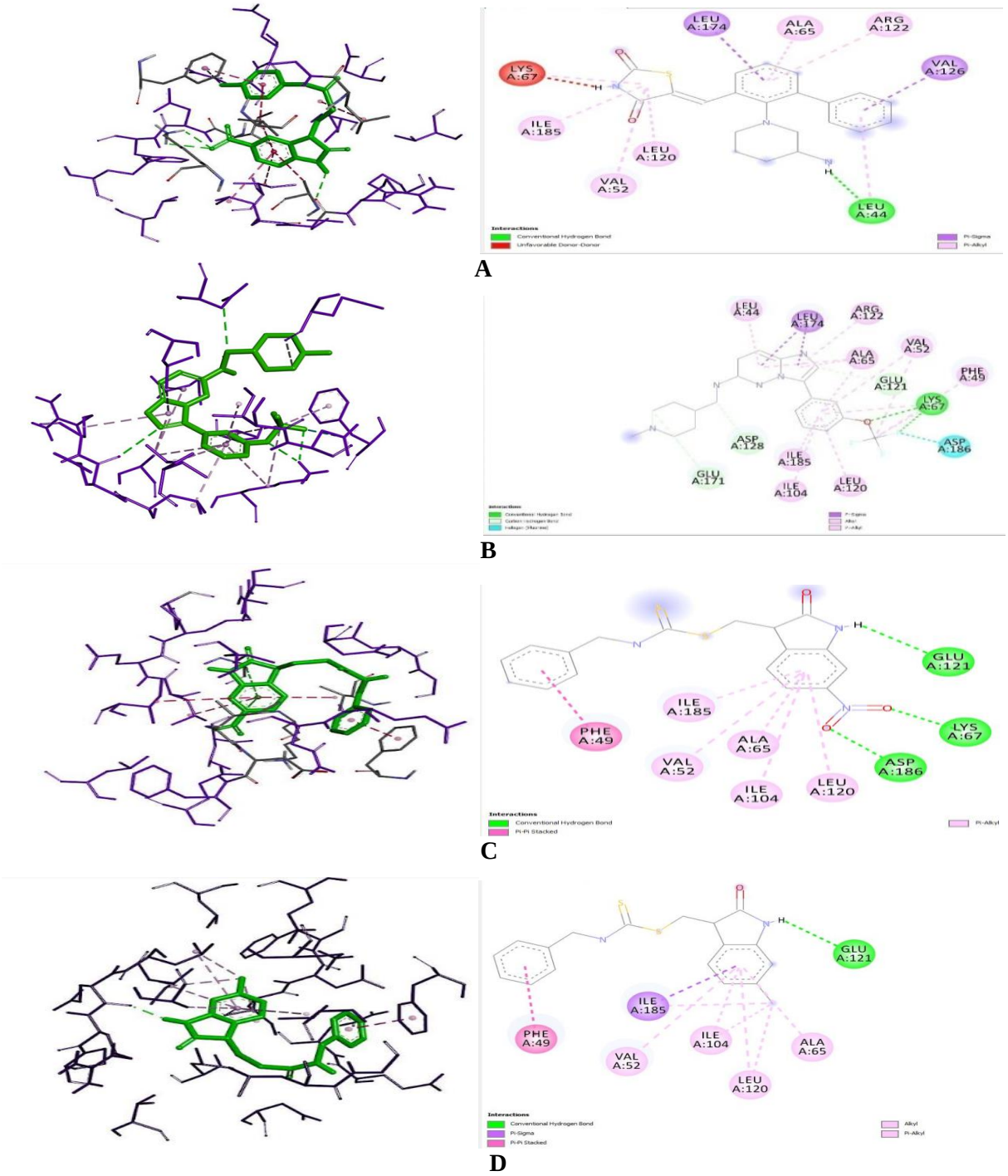


Figure 2. The 3D and 2D docking mode of ligands (A) AZD1208 (B) SGI1776 (C) Compound 16 (D) Compound 24, into PIM1 Kinase (pdb code: 3BGQ) showing hydrogen bonds (—), hydrophobic interactions (— — —)

PIM (Pro-viral integration site in Moloney murine leukemia virus) kinases are a family of serine/threonine protein kinases that are identified as unique molecular targets in oncogenesis and highly expressed in numerous human cancers. In connection with literature, a new series of 2-oxindole based

dithiocarbamate derivatives was designed and performed *in silico* experiments. The drug-likeliness assessment analysed with Molinspiration, Molsoft, Swiss ADME and pkCSM softwares, which elucidated their full compliance with Lipinski's rule, physicochemical properties and pharmacokinetic parameters. Further molecular docking study showed good binding energy for all the compounds with the human target protein PIM1 (3BGQ). Overall, the ligands 16 and 24 exhibited the equivalent binding energies of -9.7 kcal/mol when compared to known reference compound AZD1208 (-9.7 kcal/mol). These results suggested that this study will help in designing of novel derivatives of dithiocarbamate substituted 2-oxindole in discovery of new chemical entities for anticancer therapy.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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