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Molecular Docking and ADMET Study of Quinoline-based Derivatives for Anti-Cancer Activity

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ABSTRACT

An In silico study was carried out on a series of novel quinoline based inhibitors which were designed, synthesized and assessed for their in vitro activity versus the human colon cancer cell line HT29 and the human breast cancer cell line MDA-MB231 by Arafa RK et. al. We have designed these 22 inhibitors in ChemBioOffice 2010 and minimized using the LigPrep tool of Schrödinger 2011. Docking study of these inhibitors was performed on different cancer proteins in order to give a suggestion to the proposed *in vitro* mechanism of action. Some prominent cancer proteins specifically causing breast and colon cancers are used as targets in this computational study to predict the most active quinoline based derivative. The proteins are minimized using the protein preparation wizard and Grid is generated by specifying the active site amino acids. The binding model of best scoring inhibitor with each protein was assessed from their G-scores and disclosed by docking analysis using the XP visualizer tool. Interestingly the result of docking was found to match with the previous invitro study where the most active derivative against both tested cell lines was the Schiff's base *4e*. The pharmacokinetic parameters study was done using the QikProp 3.4 tool to display ADME and toxicity properties of these inhibitors.

INTRODUCTION

Cancer results from uncontrolled growth of abnormal cells in the body and is the major cause of death worldwide. Cancer starts from normal cells which are our body's building blocks. Normal cells divide and grow in order to maintain the cell population equilibrium and to balance cell death. Cancer occurs when unbounded growth of cells in the body happens fast. It can also occur when cells lose their ability to die. Cancer can develop in almost any organ or tissue. There are many different kinds of cancers, such as lung, colon, breast, skin, bones, or nerve tissue. There are many known causes of cancers like exposure to chemicals, drinking excess alcohol, excessive sunlight exposure, and genetic differences, to name a few [1].

Many natural, semi-synthetic and synthetic derivatives based on quinoline scaffold are found to have established anti-tumor activity through inhibition of several cancer proteins and have demonstrated high anti-proliferative activity by employing various mechanisms of action. The natural alkaloid Camptothecin is considered as potential inhibitor for the nuclear enzyme DNA topoisomerase I. It is found that increased level of topoisomerase I enzyme is found in advanced stages of human colon adenocarcinoma and in xenografts of colon cancer [2, 3]. Topoisomerase IIα (topo IIα) plays a key role in

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DNA replication and is a target for multiple chemotherapeutic agents in breast cancer. Studies show a significant association of increased expression of topo IIα enzyme in primary breast cancers. This may indicate a potential role of topo IIα as a prognostic marker in breast cancer [4, 5].

There are numerous other reports which reveal the inhibitory activity of novel quinoline derivatives through variable mechanism against several cancer causing proteins. Inhibition of carbonic anhydrase II plays a key role in treatment of cancer. Some novel quinoline and pyrimidoquinoline derivatives having a sulfonamide moiety were synthesised by Ghorab MM et. al and the newly synthesized compounds were evaluated for their in vitro anticancer activity against carbonic anhydrase II and also by docking studies [6]. Carbonic anhydrase isoenzymes I & II are present in colorectal cancer but in most of the cases isoenzyme I is not expressed. Therefore in our docking study we have used carbonic anhydrase isoenzyme II (PDB ID: 3KS3) as one of the targets [7, 8]. Quinoline based derivatives are potential inhibitors of carbonic anhydrase isoenzymes and play important role in treatment of breast cancer [9]. A polymorphism in the manganese superoxide dismutase (MnSOD) gene, Ala-9Val, has been examined in association with breast cancer risk in several epidemiologic studies [10]. Also study has shown higher superoxide dismutase activity in tissues of human colorectal cancers. Quinoline derivatives inhibited the growth of cancer cells through their effect as free-radical regulators by increasing the activity of superoxide dismutase activity [11, 12]. Structure-based virtual screening study of a series of quinolyl-thienyl chalcones was carried by Rizvi SU et. al which indicated their strong potential as VEGFR-2 kinase inhibitors [13]. Functional studies revealed that chronic inflammation leads to an up-regulation of VEGFR II on intestinal epithelial cells. It is found that VEGFR-signaling acts as a direct growth factor for tumor cells in colitis associated cancer providing a molecular link between inflammation and the development of colon cancer [14].

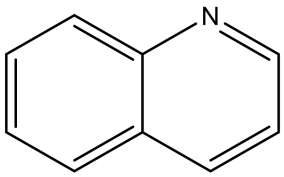
In silico molecular modeling and docking studies have considerably increased to predict potential inhibitors (drugs) for the treatment of several diseases. Homology modeling, Docking, quantitative structure activity relationships (3D QSAR), virtual ligand screening, similarity and pharmacophore searching, data mining, and data analysis tools are becoming increasingly important In silico approaches in new drug design and have been frequently used in the discovery and optimization of novel molecules with enhanced affinity and specificity for the selected therapeutic targets. The computational process by which we can assess the complementary aspects between a ligand and a receptor binding site has been explored with the design of specifically dedicated computational technique like docking. Early docking methods were based uniquely on assessing the shape complementarity between a pocket in the 3D structure of a protein and low energy conformers of a ligand [15-17]. Today there is a considerable increment in the application of in silico molecular modeling and docking studies to predict potential inhibitors (drugs) for the treatment of several diseases [18]. Further computational prediction of pharmacokinetic parameters like Absorption, Distribution, Metabolism and Excretion (ADME) & toxicity studies have become increasingly important in drug selection and promotion process and are promising tools for early screening of potential drug candidates [19].

We performed a docking study of 22 quinoline based derivatives against few cancer proteins to check their inhibitory activity and also to evaluate their binding interactions with these proteins using computational tools [20]. The results have been confirmed by the G Scores obtained from Grid – based Ligand Docking with Energetics (GLIDE) of Schrödinger 2011 [21, 22].

Materials and Methods

Selection of target proteins

Following seven cancer proteins with their resolutions and ligand interaction diagram as retrieved from the data bank



quinoline

Figure 1: Structure of quinoline

Table 1: Proteins used as target in the docking study

S.No	Protein PDB ID	X-ray Resolution [Å]	Active site amino acid
1	Carbonic anhydrase II (3KS3)	0.90	Tyr 7A
2	C-MET (4GG7)	2.27	Asp1222A
3	Topoisomerase I (1K4T)	2.10	Lys532A
4	Topoisomerase II (1ZXM)	1.87	Gly161A
5	Superoxide dismutase (4A7U)	0.98	Ser102A
6	Tubulin (4B5O)	1.05	Gly136A
7	VEGFR II (3VHE)	1.55	Glu885A

(PDB) (www.rcsb.org/pdb) are targeted in this study (Table: 1). Structural and active site studies of the protein were done by using CASTp (Computed Atlas of Surface Topography of Proteins).

Molecules information

A series of 22 quinoline based inhibitors are retrieved from the available article *by* Arafa RK *et al.* It has been concluded from their work that quinoline based compounds are potent inhibitor for several cancer proteins. Among the 22 compounds that we have subjected for docking and post docking analysis, six are quinoline based anti cancer compounds and 16 are new synthesized quinoline derivatives.

Table 2: The LigPrep 2.5 result showing conformers with least potential energy

S.No	Ligand	Potential energy-OPLS-2005 (Kcal/mol)
1	4a	94.87197
2	4b	93.24479
3	4c	92.86926
4	4d	104.0778
5	4e	123.8433
6	4f	109.3086
7	5a	113.7276
8	5b	111.6049
9	5c	122.7603
10	6a	116.2232
11	6b	135.4021
12	7a	126.8738
13	7b	149.4981
14	8	72.07941
15	9	100.7234
16	10	95.97635
17	Camptothecin	212.9464
18	I	99.31337
19	MS-209	266.9231
20	MT-477	367.0873
21	TAS-103	173.117
22	Topotecan	201.8601

Protein Preparation & Active site prediction

Prior to docking, it is important to identify the binding site in the target protein. The predicted ligand binding site residues in each protein was predicted from the ligand interaction diagram. The PDB structure files of the proteins are downloaded in PDB format. The processing, optimization and minimization of these proteins is carried out in the protein preparation wizard of the Schrödinger2011 by applying the OPLS_2005 force field and active site amino acid in all proteins are specified for the receptor grid generation.

Molecules Preparation

The 22 compounds were designed in ChemBioOffice 2010 software and obtained in .mol format and used as input structures for processing in LigPrep 2.5 for geometry optimization and energy minimization which is run from Maestro9.2 of Schrödinger2011. Among many conformers obtained in the LigPrep, the conformer with least potential energy (Table: 2) are subjected to Impact minimization module under the applied OPLS_2005 force field. The significance of impact minimization is to observe the Lennard Jones Energy, which should be in negative. The Impact minimized molecules are further subjected for the docking study.

Docking

Docking studies are computational techniques for exploration of possible binding mode of a substrate to a given receptor, enzyme or other binding site. The docking studies of the above 22 molecules with the seven different oncoproteins is performed using the GLIDE 5.7 module. Overall, the Vander Waals energy contributed most to the interaction energy, but the electrostatic energy showed the greatest variation and was therefore the major factor for the ranking of molecules. Docking result revealed that all the molecules were docked efficiently as it is evident from the XP Glide scores(*see table: 3*). The top five molecules showing highest XP G scores with each protein are highlighted in blue color and the molecule *4e* is found to give highest score with three of the proteins used as targets. Dock result of *4e* with other four proteins is also exceptionally good and proves it to be a significant *quinoline based scaffold* for anti-proliferative activity.

ADME & Toxicity Studies

The ability to detect problematic candidates early can dramatically reduce the amount of wasted time and resources, and streamline the overall drug development process. ADME (Absorption, Distribution, Metabolism and Excretion) studies are carried out in the QikProp3.4 for assessing the disposition and potential toxicity of ligand with in an organism. The overall pharmacological properties (Tables 5(A) & 5(B)) of these molecules justify that the molecules are biologically active without any toxic functional groups.

Table 3: Docking result showing XP G scores of all the 22 drug molecules with seven oncoproteins

S.No	Drug Molecule	C-MET	Super oxide dismutase	Tubulin	VEGFR	Carbonic anhydrase	Topoisomerase I	Topoisomerase II
		4GG7	4A7U	4B5O	3VHE	3KS3	1K4T	1ZXM
1	4a	-5.5	-2.22	-7.93	-7.92	-4.1	-5.02	-5.41
2	4b	-6.83	-2.30	-7.17	-8.99	-5.20	-4.43	-6.21
3	4c	-5.39	-2.18	-7.82	-8.88	-4.09	-4.56	-4.74
4	4d	-5.16	-2.85	-7.99	-8.19	-0.73	-4.39	-6.24
5	**4e**	**-5.63**	**-5.12**	**-7.90**	**-9.02**	**-5.20**	**-5.49**	**-7.89**
6	4f	-6.52	-2.24	-8.07	-8.73	-4.14	-4.57	-5.65
7	5a	-5.78	-3.04	-6.86	-7.44	-4.70	-4.53	-4.44
8	5b	-6.33	-3.05	-7.72	-8.08	-3.60	-4.82	-5.89
9	5c	-6.44	-2.88	-7.67	-7.52	-3.78	-5.06	-6.12
10	6a	-6.85	-3.29	-6.53	-6.08	-5.03	-3.34	-5.14
11	6b	-6.83	-1.47	-5.02	-7.05	-5.04	-2.53	-5.32
12	7a	-6.49	-1.53	-5.42	-6.26	-3.08	-2.91	-5.40
13	7b	-5.09	-1.08	-5.71	-4.85	-2.56	-4.88	-3.81
14	8	-4.77	-1.86	-4.51	-5.43	-3.01	-3.75	-6.10
15	9	-6.19	-2.79	-6.98	-5.78	-3.37	-5.22	-5.66
16	10	-6.34	-1.93	-7.7	-4.09	-3.09	-6.57	-2.92
17	Camptothecin	-4.79	-2.94	-7.49	-6.51	-5.47	-4.69	-6.31
18	I	-5.79	-3.0	-7.15	-4.55	-3.17	-5.07	-3.33
19	MS-209	-3.52	-2.69	-5.13	-7.51	-3.79	-3.86	-2.88
20	MT-477	-2.12	-0.92	-2.09	-4.04	-3.10	-5.27	-
21	TAS-103	-6.68	-2.48	-6.0	-4.40	-3.28	-5.91	-3.88
22	Topotecan	-5.31	-3.25	-5.18	-4.45	-6.97	-3.76	-5.19

(Scores of five best molecules are indicated in blue color and the score of 4e with all protein is indicated in green)

Results

The docking result in the form of XP G scores of the 22 derivatives with seven different oncoproteins C-MET (3KS3), Super oxide dismutase (4A7U), Tubulin (4B5O), VEGFR (3VHE), Topoisomerase I (1K4T) and Topoisomerase II (1ZXM) are tabulated in the *table 3*. The stability of docking between ligand and the target protein depends on the binding interactions and thus the G score describes how well the drug has interacted with the protein. In the table 3, the G scores of five best scoring molecules with each of the proteins are shown in blue color. The molecule *4e* is among the five best scoring ligands with all proteins. The hydrogen bonding interaction which is a vital parameter for the stability of *drug-protein complex* is found in all the best scoring molecules as a result of docking. The binding interaction of highest scoring molecule with active site amino acids of each protein used as target is depicted in the docking images along with their respective bond distances as

Table 4: QikProp properties and descriptors.

Property or Descriptor	Description	Range or recommended value
#stars	A large number of stars suggest that a molecule is less drug-like than molecules with few stars.	**0 – 5**
CNS	Predicted central nervous system activity on a –2 (inactive) to +2 (active) scales.	**–2 (inactive), +2 (active)**
mol_MW	Molecular weight of the molecule.	**130.0 – 725.0**
dipole	Computed dipole moment of the molecule	**1.0 – 12.5**
SASA	Total solvent accessible surface area (SASA) in square angstroms using a probe with a 1.4 Å radius	**300.0 – 1000.0**
volume	Total solvent-accessible volume in cubic angstroms using a probe with a 1.4 Å radius	**500.0 – 2000.0**
donorHB	Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution.	**0.0 – 6.0**
accptHB	Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution.	**2.0 – 20.0**
QPlogPoct	Predicted octanol/gas partition coefficient	**8.0 – 35.0**
QPlogPw	Predicted water/gas partition coefficient	**4.0 – 45.0**
QPlogBB	Predicted brain/blood partition coefficient	**–3.0 – 1.2**
IP(ev)	PM3 calculated ionization potential	**7.9 – 10.5**
EA(eV)	PM3 calculated electron affinity	**–0.9 – 1.7**
HumanOralAbsorption	Predicted qualitative human oral absorption: 1, 2, or 3 for low, medium, or high.	
PercentHuman-OralAbsorption	Predicted human oral absorption on 0 to 100% scale	**>80% is high <25% is poor**
PSA	Van der Waals surface area of polar nitrogen and oxygen atoms	**7.0 – 200.0**
RuleOfFive	Number of violations of Lipinski's rule of five	**maximum is 4**
RuleOfThree	Number of violations of Jorgensen's rule of three	**maximum is 3**

shown in Figures 2(a), 2(b) & 2(c).

The ADME and toxicity result of all the molecules computed in Qikprop 3.4 properties and descriptors are falling within the range or are the recommended values as shown in table 4.

Discussion

The binding interaction between the ligand molecule and protein has a significant role in determining the activity and binding potential of the drug in computational study. The docking and post docking analysis of 22 quinoline based inhibitors synthesized by *Arafa RK et.al* was carried out using computational tools and techniques. In their study these derivates were assessed for their invitro activity on human colon cancer cell line HT29 and breast cancer cell line MDA-MB231, therefore our goal was to target few protein involved in colon and breast cancers. Interestingly the result of docking was found to match with the previous invitro study. According to their biological study molecule 4e was found be most active derivative against both tested cell lines. In our study also the derivative 4e has shown highest G-score with 4A7U, 1ZXM and 3VHE proteins. Moreover when we analysed the top five scoring inhibitors with each protein, molecule 4e showed exceptionally good docking score, which shows that 4e is a potential inhibitor and is an important molecule for researchers to develop cancer

Figure 2(a): Docking image of 4e with 1K4T

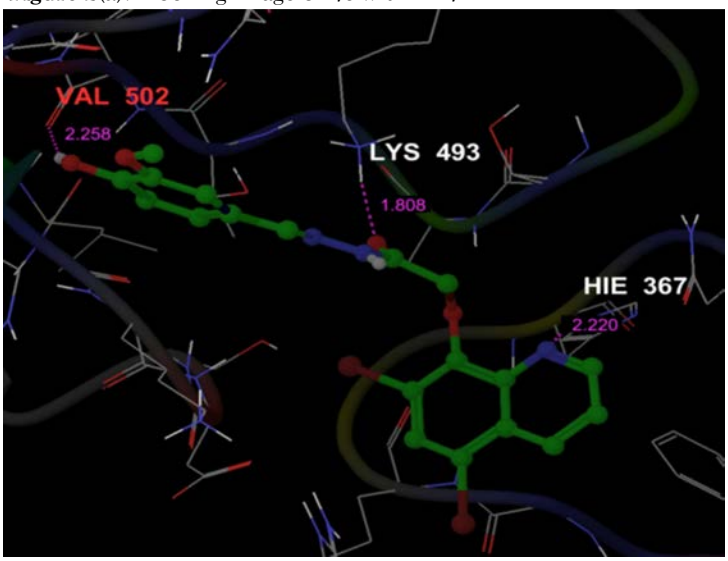


Figure 2(b): Docking image of 4e with 1ZXM

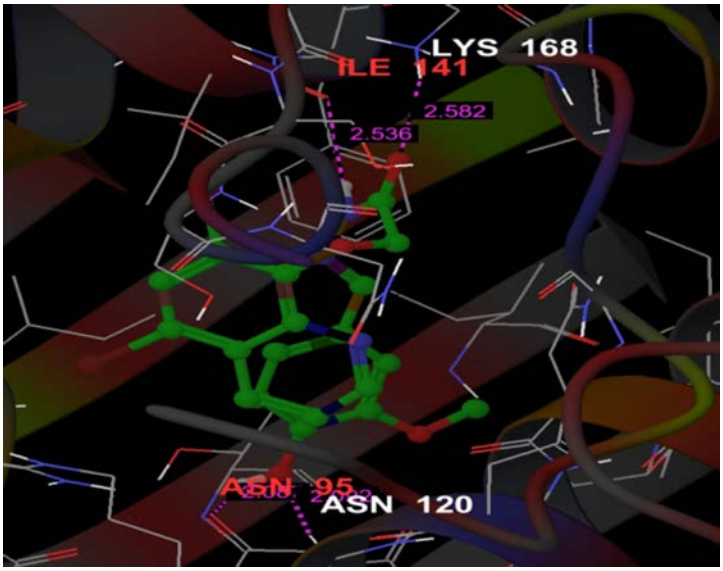
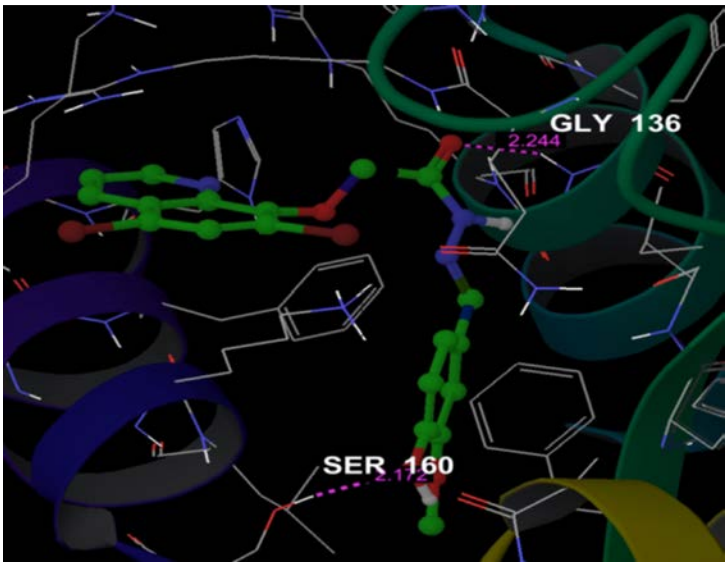


Figure 2(c): Docking image of 4e with 4B5O



drugs. The ADME and toxicity study was computed using the QikProp3.4. All pharmaco-kinetic parameters of the 22 derivatives used in the study were found to be within the range or are the recommended values to become a potent inhibitor.

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Table 5 (A): Predictions of ADMET pharmacological properties for the 22 molecules by QIKPROP 3.4

Molecule	#stars	CNS	mol_MW	dipole	SASA	volume	donorHB	accptHB	QPlogPoct
4a	1	0	463.128	8.745	612.429	1080.98	1	4.25	17.292
4b	2	0	497.573	9.519	636.626	1125.352	1	4.25	18.144
4c	2	0	542.024	9.385	641.698	1134.305	1	4.25	18.25
4d	2	-2	508.125	12.939	650.869	1153.995	1	5.25	19.774
4e	1	0	509.153	6.971	658.767	1174.959	2	5.75	19.718
4f	1	0	493.154	7.583	648.176	1155.018	1	5	17.892
5a	1	0	477.154	8.463	633.265	1129.872	1	3.75	17.502
5b	3	1	556.05	9.394	662.401	1183.022	1	3.75	18.516
5c	2	-2	522.152	13.395	671.575	1202.81	1	4.75	20.14
6a	0	-1	494.142	3.091	675.06	1167.334	1.5	4.75	19.107
6b	0	-1	510.202	3.095	674.708	1183.028	2.25	6	21.114
7a	1	0	476.126	12.614	504.473	984.057	1	3.75	17.246
7b	2	1	492.187	10.273	514.443	1017.285	0.8	3.75	16.703
8	1	1	417.074	7.761	521.731	883.881	0.8	4.25	14.321
9	0	1	439.106	8.645	594.079	1034.918	0	5.25	15.798
10	0	0	441.078	9.495	582	1005.802	0	4.25	15.035
Camptothecin	0	-1	348.357	10.467	578.408	1027.265	1	7.75	19.044
I	0	0	301.385	2.432	609.942	1068.016	0	3.75	12.87
MS-209	1	1	481.593	6.864	745.46	1455.878	1	8.45	23.851
MT-477	2	-2	718.764	6.569	990.137	1923.786	0	15.75	31.801
TAS-103	0	1	333.389	2.558	594.137	1058.107	1	5.25	15.989
Topotecan.mol	0	-2	421.452	7.75	683.739	1246.773	2	10.5	23.133

Table 5 (B): Predictions of ADMET pharmacological properties for the 22 molecules by QIKPROP 3.4

Molecule	QPlogPw	QPlogBB	IP (eV)	EA (eV)	Human Oral Absorption	Percent Human Oral Absorption	PSA	RuleOf Five	RuleOf Three
4a	8.582	-0.189	8.733	1.802	3	100	63.443	0	0
4b	8.343	-0.029	8.756	1.84	1	100	63.436	1	1
4c	8.352	-0.019	8.86	1.849	1	90.941	63.434	2	1
4d	9.7	-1.242	9.344	1.983	3	79.935	108.331	1	0
4e	10.908	-0.694	8.422	1.772	3	91.372	90.031	1	0
4f	8.804	-0.268	8.511	1.784	3	100	71.867	0	0
5a	7.989	-0.113	8.65	1.751	3	100	60.29	1	1
5b	7.759	0.058	8.778	1.798	1	95.585	60.29	2	1
5c	9.107	-1.174	9.226	1.925	3	84.552	105.205	1	1
6a	11.826	-0.862	8.736	1.46	3	96.373	105.753	0	1
6b	12.662	-0.377	8.652	1.532	1	93.693	84.547	1	1
7a	7.67	-0.151	9.284	1.579	3	100	71.314	0	0
7b	7.016	0.363	9.13	1.586	3	100	49.883	0	0
8	7.366	0.237	9.279	1.512	3	100	57.706	0	0
9	7.701	0.068	9.036	1.438	3	100	59.874	0	0
10	6.774	-0.347	9.185	1.463	3	100	82.031	0	0
Camptothecin	12.356	-0.783	9.097	1.652	3	86.05	95.983	0	0
I	5.129	-0.27	8.927	1.203	3	100	50.293	0	0
MS-209	14.969	-0.484	8.612	0.834	3	90.405	65.324	0	1
MT-477	18.186	-2.51	8.919	1.618	2	48.672	214.604	2	1
TAS-103	9.306	-0.184	8.381	1.602	3	89.442	76.322	0	0
Topotecan	15.711	-1.093	8.811	1.475	3	64.133	119.283	0	0

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