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ORIGINAL PAPER

Identification of potential oral cancer drugs as Bcl-2 inhibitors from known anti-neoplastic agents through docking studies

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Abstract

Oral Cancer is one of the major killers in India and of global concern. An attempt has been made here to identify small molecule inhibitors of Bcl-2 (B-cell lymphoma 2) protein through docking studies in search of new oral cancer drugs from a curated set of 276 known anti-neoplastic agents obtained from PubChem. The Bcl-2 protein (PDB id:6QGH), being complexed with ligand ABT-263, has been detached from the complex. The ligand-free protein and 276 compounds have been prepared for docking studies using corresponding tools available in Discovery Studio (DS), ver.4.1. The 276 compounds have been docked on the first site of the protein using LibDock docking program available in DS. By considering Methotrexate as the reference compound (LibDock score: 114.76), we have identified 25 compounds as the most potential oral cancer drugs having LibDock scores greater than 100. Another set of 114 compounds with LibDock scores between 80 and 100 have also been identified as the next set of potential drug candidates and some of them show anti-apoptosis properties. Two other compounds with LibDock scores below 80 have been identified for comparative analyses with some high-scoring compounds. The docking results have been given in tables and pictures (screenshots) of the docked poses of selected compounds have been shown to illustrate the findings. Finally, the most suitable potential compounds have been identified by applying Lipinski's Rule of 5. The present approach using known anti-neoplastic agents is believed to help discover potential anti-oral cancer drug candidates.

Keywords Bcl-2 protein inhibitors · Potential oral cancer drugs · Anti-neoplastic compounds · Docking studies · Lipinski's rule-of five

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1 Introduction

It is more than 30 years [1] that Bcl-2 (B-cell lymphoma 2) has been studied in search of anti-cancer drugs. The reason is linked to its role in apoptosis (programmed cell death) [2]. Among many aspects which have been studied [3, 4], finding small molecule inhibitors of Bcl-2 proteins has drawn special attention for discovering anti-cancer drugs [5, 6]. Such compounds are potential candidates for various cancer treatments [5, 7, 8]. More recently, interest has been shown to discover Bcl-2 inhibitors as anti-oral cancer drugs [9–12]. Various computational methods have been used in this purpose, although structure-based design (SBD) methods have been used widely perhaps due to the ability of such methods to study drug-receptor interactions helping understand drug activity more clearly. It is noteworthy that one of the most useful Bcl-2 protein inhibitors, an ABT series of drugs, ABT-263 (Navitoclax), has been discovered using SBD methods [5].

As of now, researchers have worked on discovering new series of compounds as Bcl-2 inhibitors [5–12]. However, we aim to evaluate known anti-neoplastic agents as Bcl-2 protein inhibitors in search of potential anti-oral cancer drugs. This approach is believed to help identify potential compounds differently from a carefully curated important set of known anti-neoplastic agents. Therefore, we have compiled a set of 276 such compounds taken from PubChem [13] and the compounds have been docked on a human Bcl-2 protein (PDB id: 6QGH), taken from Protein Data Bank (PDB) [14] using LibDock small molecule docking program available in Discovery Studio (DS) (ver. 4.1) [15]. The protein is complexed with a ligand ABT-263. Therefore, the ligand has been detached first and then the ligand-free protein and 276 compounds, collected from PubChem [13], have been prepared for docking using corresponding tools available in DS (ver. 4.1) [15].

For carrying out the docking studies, we have considered Methotrexate, a well-known anti-cancer drug, as a reference compound having a LibDock score of 114.76. Subsequently, 25 compounds that have returned scores higher than 100 (> 100) have been identified as the high-scoring compounds, and 114 compounds that produced LibDock scores between 80 and 100 have been identified as the next level of high-scoring compounds. The main reason for identifying the next level of high-scoring compounds is the apoptosis-related property that several compounds in this set possess and therefore can be of interest for the present purpose. Moreover, their scores are not too low either (compared to the high-scoring compounds) unlike those obtained for many other low-scoring compounds considered for the present docking studies. The results of these two sets of high-scoring docked compounds are given in two tables (Tables 1 and 2). The drug-receptor interactions have also been carried out for selected high-scoring compounds as well as some low-scoring compounds and that has been illustrated with docked poses along with the interacting bonds for the compound giving the highest LibDock score as well as those for a low-scoring compound for having a comparative picture. Finally, a set of 10 most probable potential anti-oral cancer drug candidates have been identified based on Lipinski's Rule-of-Five [16] filtering and a few other considerations [13] from the compounds given in Tables 1 and 2.

Table 1 The 25 anti-neoplastic agents as potential Bcl-2 inhibitors with LibDock scores greater than 100

Serial no.	Compound name	PubChem CID	LibDock score
1.	Methotrexate (Reference compound)	126,941	114.76
2.*	Olaparib	23,725,625	124.36
3.	Delta-12-Prostaglandin J2	5,280,885	123.16
4.	Raltitrexed	135,400,182	119.25
5.**	Seliciclib	160,355	116.65
6.	Pemetrexed	135,410,875	114.20
7.	Lometrexol	135,413,518	113.82
8.**	Bortezomib	387,447	112.64
9.	Piritrexim	54,369	107.65
10.	Voruciclib	67,409,219	107.30
11.	Apatinib	11,315,474	106.01
12.	Cyproteroneacetate	9880	105.53
13.	Banoxantrone	9,955,116	104.69
14.	Fluvastatin	446,155	104.06
15.***	Amrubicin	3,035,016	103.66
16.	Teroxirone	17,142	103.58
17.***	Filanesib	44,224,257	102.98
18.	Curcumin	969,516	102.91
19.	Pixantrone	134,019	102.42
20.**	Panobinostat	6,918,837	102.40
21.	Ritrosulfan	142,773	102.18
22.	Salirasib	5,469,318	101.15
23.*	Artesunate	60,196,289	100.84
24.*	Belinostat	6,918,638	100.64
25.*	Cephalotaxine	278,679	100.10

*Apoptosis inducer (Nos. 2, 23, 24, 25), **Apoptotic activity (Nos. 5, 8. 20), ***Plays a role in cell death (Nos. 15, 17)

2 Methods

We have carried out the docking studies using LibDock, a small molecule docking program, available in DS (ver. 4.1) software [15]. The LibDock docking program is based on a binding site comprising of lists of polar and apolar hot spots [15]. To carry out the docking studies, we have considered a human Bcl-2 protein obtained from Protein Data Bank (PDB id: 6QGH) [14] complexed with a ligand ABT-263. The ligand ABT-263 has been detached to get the ligand-free protein for docking studies. A set of 276 known anti-neoplastic compounds, carefully curated from PubChem [13], have been considered for docking. In this docking study, the receptor is fixed and the ligands/small molecules are flexible which allows the generation of several conformations/poses. The docking studies have been carried out using the default parameters, e.g., Number of Hotspots: 100; Docking Preference:

Table 2 A list of 114 Bcl-2 inhibitors with LibDock scores between 80 and 100 and 2 inhibitors with scores less than 80 (the last two compounds underlined)

Serial no.	Compound name	PubChem CID	LibDock score
1.	Anastrozole	2187	99.91
2.	Fludarabine	657,237	99.62
3.	Picibanil	640,429	99.43
4.	Dofequidar	213,040	99.32
5.	NECA	448,222	99.17
6.	Prospidium	31,938	99.17
7.	Acronine	345,512	99.12
8.#	Entinostat	4261	98.99
9.#	M 344	3994	98.68
10.	Bufalin	9,547,215	98.62
11.#	ICRF-193	119,081	98.44
12.#	Vidarbine	40,926	98.21
13.	Clofarabine	119,182	98.17
14.	Batimastat	5,362,422	97.98
15.	Nafazatrom	52,923	97.85
16.#	Cladribine	20,279	97.43
17.#	Bendamustine	65,628	97.20
18.	Razoxane	30,623	97.15
19.#	Alvocidib	5,287,969	96.98
20.#	Ixazomib	25,183,872	96.93
21.#	Inolitazone	9,832,447	96.92
22.#	Tocladesine	100,299	96.79
23.	Anaxirone	71,218	96.56
24.#	Bicalutamide	2375	96.08
25.	Melphalan	460,612	95.74
26.	N(1),N(12)-Diethylspermine	4283	95.73
27.#	Vorinostat	5311	95.12
28.	Rucaparib	9,931,954	94.98
29.	Camptothecin	24,360	94.90
30.#	Staurosporine	451,705	94.62
31.	Melphalan	460,612	94.62
32.	Gefitinib	123,631	94.40
33.	Mitonafide	327,044	94.40
34.	Epothilone A	448,799	94.31
35.	Tnp-470	369,976	94.15
36.	Formycin A	447,199	94.06
37.	Dexrazoxene	71,384	94.01
38.	Pentostatin	439,693	93.82
39.#	Pomalidomide	134,780	93.30
40.	Sparsomycin	9,543,443	92.94
41.#	Idelalisib	11,625,818	92.87

Table 2 (continued)

Serial no.	Compound name	PubChem CID	LibDock score
42.	Diindolylmethane	3071	92.72
43.#	Rigosertib	6,918,736	92.69
44.	Glarubin	441,794	92.53
45.	Amonafide	50,515	92.52
46.	Puromycin	439,530	92.49
47.	Epipodophyllotoxin	105,111	92.41
48.	Chlorambucil	2708	92.40
49.	Etoglucid	16,058	92.36
50.	Cordycepin	6303	92.01
51.#	Thioinosine	676,166	91.76
52.	Daca	107,805	91.45
53.#	Lenalidomide	216,326	91.12
54.	Erlotinib	176,870	91.03
55.	Elliptinium	42,723	90.86
56.	Vadimezan	123,964	90.51
57.	Tiazofurine	457,954	90.37
58.	Cytarabin	596	90.27
59.	Letrozole	3902	90.13
60.	Trimetrexate	5583	90.11
61.	9-Aminocamptothesin	72,402	89.84
62.	Formestane	11,273	89.82
63.	Amsacrine	2179	89.77
64.#	Genistein	5,280,961	89.72
65.	9-Hydroxyellipticine	91,643	89.63
66.	Tesevatinib	10,458,325	89.46
67.	Mafosfamide	104,746	89.40
68.	Gemcitabine	60,750	89.33
69.	Ellipticine	3213	88.85
70.	O6-Benzylguanine	4578	88.44
71.	Niraparib	24,958,200	88.42
72.	Carmofur	2577	88.35
73.	Cediranib	9,933,475	88.06
74.#	Hexamethylene Amiloride	1794	87.92
75.	Carboquone	2569	87.82
76.#	Tyrphostin B42	5,328,779	87.47
77.	Fazarabine	47,751	87.37
78.#	2-Methoxyestradiol	66,414	87.20
79.#	Sulindac	1,548,887	87.20
80.#	Sulindac Sulfone	5,472,495	87.13
81.	Combretastatin	335,929	87.12
82.	Sulofenur	60,417	86.90
83.	Indisulam	216,468	86.75

Table 2 (continued)

Serial no.	Compound name	PubChem CID	LibDock score
84.	Cytarabine	6253	86.64
85.	Veliparib	11,960,529	86.58
86.	Fotemustine	104,799	86.57
87.#	Trichostatin A	444,732	86.54
88.#	Nitracrine	20,628	86.51
89.	Apaziquone	5,813,717	86.34
90.#	Imiquimod	57,469	86.33
91.	Topotecan	60,700	86.31
92.	Aminoglutethimide	2145	86.03
93.	Halofuginone	400,772	85.94
94.	Nolatrexed	135,400,184	85.93
95.	Trofosfamide	65,702	85.86
96.	Troxacitabine	454,194	85.79
97.	Procarbazine	4915	85.48
98.	Decitabine	451,668	85.32
99.	Ancitabine	25,051	85.14
100.#	Devazepide	443,375	84.96
101.	Chelerythrine	2703	84.86
102.	LY-83,583	3976	84.55
103.	Helenalin	23,205	84.34
104.	NSC-668,281	381,525	84.15
105	Nimustine	39,214	83.84
106.	Streptozocin	29,327	83.68
107.	Nilutamide	4493	83.52
108.#	Sulindac Sulfide	5,352,624	82.82
109.	Dasatinib	3,062,316	82.2
110.	Mitozolomide	71,766	82.07
111.	Treosulfan	9,882,105	82.06
112.	Roquinimex	54,676,478	81.80
113.	Diethylstilbestrol	448,537	81.71
114.	Dabrafenib	44,462,760	80.41
115.	Lenvatinib	9,823,820	77.89
116.	Tucatinib	51,039,094	54.80

#Apoptosis inducer

High Quality, onto the first site in the protein molecule identified by the site finding tool available in DS (ver. 4.1) [15]. Subsequently, some selected compounds have been filtered through Lipinski's "Rule-of-5" (Molecular Weight (MWT) not greater than 500; Calculated Partition Co-efficient, Clog P, not greater than 5.0; Hydrogen Bond Donor, NHs and OHs, not more than 5 and Hydrogen Bond Acceptor, Ns and Os, not more than 10) [16] by considering relevant PubChem [13] information to identify most probable and potential anti-oral cancer drug molecules. It may be

noted that Lipinski et al. [16] have pointed out that the compound classes that are substrates of biological transporters are exceptions to the rule. It may also be noted that although Methotrexate violates the H-bond acceptor number to some extent (12 H-bond acceptors) [13] and may also have some notable side effects, it has been considered as a reference compound since it is a well-known anti-cancer drug. Lipinski et al. [16] have shown that some existing drugs, e.g., Erythromycin (MWT = 733.95, H-bond Acceptor = 14), do not obey all four points of the Rule-of-Five.

3 Results and discussion

In this section, we have first furnished and discussed docking results obtained by docking 276 known anti-neoplastic compounds, obtained from PubChem [13], on the ligand-detached Human Bcl-2 protein (PDB id: 6QGH) [14] using the methods available in DS (ver. 4.1) [15] as described earlier. This is followed by the views (screenshots) of the docked poses and the tables on non-bonded interactions of two selected compounds, the compound that have returned the highest LibDock score and one of the low-scoring compounds, for comparative analyses. Finally, several compounds which have been screened based on their LibDock scores and apoptosis-related properties [13] have been filtered through Lipinski's Rule-of-Five [16] and some other considerations [13] to identify 10 most probable potential anti-oral cancer drug candidates based on the above-mentioned criteria adopted for the present study.

3.1 Docking and LibDock score

The 276 anti-neoplastic compounds, collected from PubChem [13] have been docked onto the first binding site, identified by the site-searching algorithm available in DS (ver. 4.1) [15], of the ligand-free Human Bcl-2 protein (PDB id: 6QGH) obtained from Protein Data Bank (PDB) [14]. To identify potential anti-oral cancer drugs, we have considered the well-known anti-cancer drug Methotrexate as a reference compound having a LibDock score of 114.76. Hence, we have first identified 25 compounds (including Methotrexate), considering them as highly potential, which have scored greater than 100 (> 100) as given in Table 1.

We have also identified a second set of 114 compounds which have returned scores between 80 and 100 (Table 2). The main reason for considering these compounds is based on the finding that several compounds of this set are apoptosis inducers and this property is believed to be an important factor for the present purpose. It has also been found that the number of apoptosis-inducing compounds having LibDock scores higher than 90 (> 90) is more in number than those having LibDock scores higher than 80 (> 80). 60 compounds have returned 90 + scores and those scores are much higher than the scores returned by several other docked compounds such as the two low-scoring compounds shown at the bottom of Table 2 (Nos. 115 and 116). Some other low-scoring compounds may possess

apoptosis-inducing properties. However, they have not been considered here as potential compounds due to their low scores.

It may also be noted that there are compounds that have not docked at all and therefore they are beyond the scope of further discussion in this paper.

3.2 Views and information for selected docked compounds

In addition to getting LibDock scores of the docked compounds, we have also taken screenshots of two docked compounds (binding pocket shown in hydrophobicity scale) along with the details of their non-bonded interactions. Accordingly, we have furnished here the above-mentioned information for the highest scoring (LibDock score) compound Olaparib (Figs. 1 and 2; Table 3) which has been taken from Table 1 (No. 2). We have also considered a low-scoring compound Tucatinib from Table 2 (No. 116) for a comparative view and analyses (Figs. 3 and 4; Tables 4, 5).**Fig. 4** Side view of docked *Tucatinib*

It is clear from Fig. 1 that the highest scoring (124.36) compound, Olaparib, has made several favorable non-bonded interactions (Fig. 1; Table 3) with the receptor protein and is found to be well placed in the binding groove (Fig. 2). On the other hand, one of the low-scoring (54.80) compounds, Tucatinib, along with forming favorable non-bonded interactions (Fig. 3; Table 4), has formed an

Olaparib:

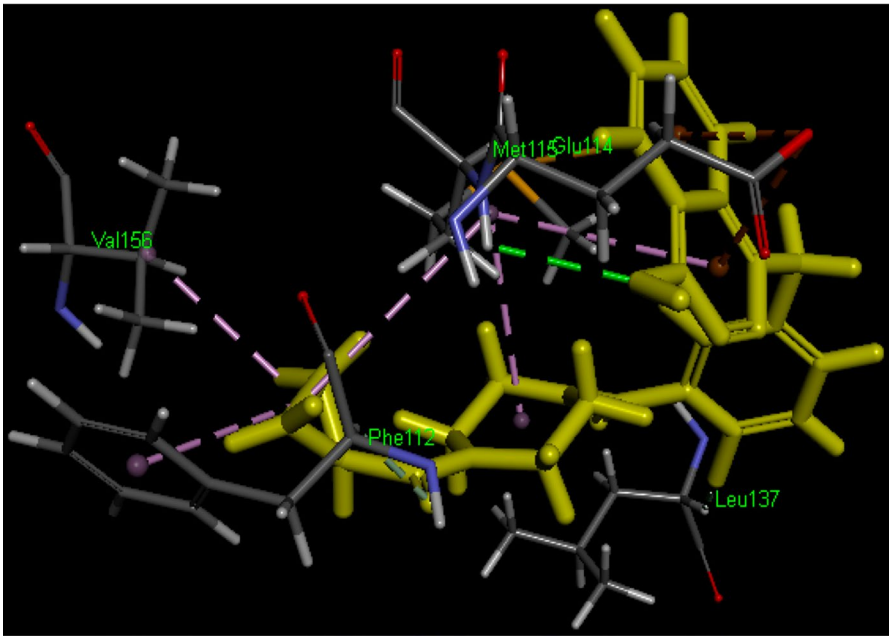

Fig. 1 Non-bonded interactions of the highest scoring pose of *Olaparib* (LibDock score: 124.36) of *Bcl-2* target protein (PDB id: 6QGH)

Table 3 Details of the non-bonded interactions of the highest-scoring pose of *Olaparib*

Serial no.	Non-bonded interaction type	Color of the bond as in Fig. 1	Non-bond between
1.	Conventional H-Bond	Green	A:MET115:HN – 23,725,625:O4
2.	Carbon H-Bond	Light Green	A:PHE112:HA - 23,725,625:O2
3.	Carbon H-Bond (Halogen: Fluorine)	Light Green	A:LEU137:HA – 23,725,625:F1
4.	Electrostatic (Pi-Anion)	Brown	A:GLU114:OE2 - 23,725,625
5.	Electrostatic (Pi-Anion)	Brown	A:GLU114:OE2 - 23,725,625
6.	Other (Pi-Sulfur)	Light Brown	A:MET115:SD - 23,725,625
7.	Hydrophobic (Alkyl)	Light Purple	A:MET115 - 23,725,625
8.	Hydrophobic (Alkyl)	Light Purple	23,725,625 – A:MET115
9.	Hydrophobic (Alkyl)	Light Purple	23,725,625 – A:VAL156
10.	Hydrophobic (Pi-Alkyl)	Light Purple	A:PHE112 - 23,725,625
11.	Hydrophobic (Pi-Alkyl)	Light Purple	23,725,625 – A:MET115

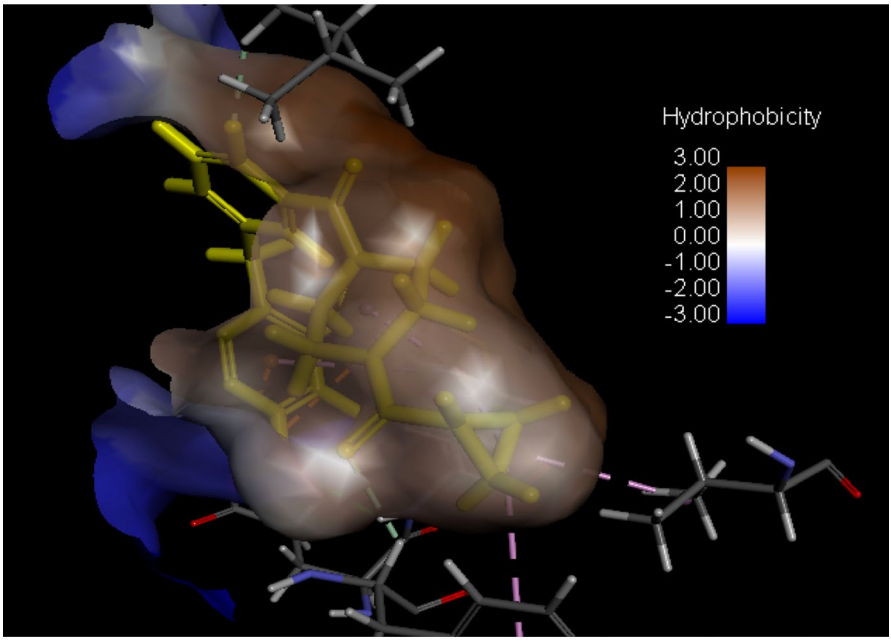

Fig. 2 Side view of docked *Olaparib*

unfavorable bond as well (Fig. 3; Table 5). Moreover, a large portion of the compound is found to be outside the binding pocket (Fig. 4). These comparative analyses seem to go along with the finding that Olaparib has got high (highest among

Tucatinib:

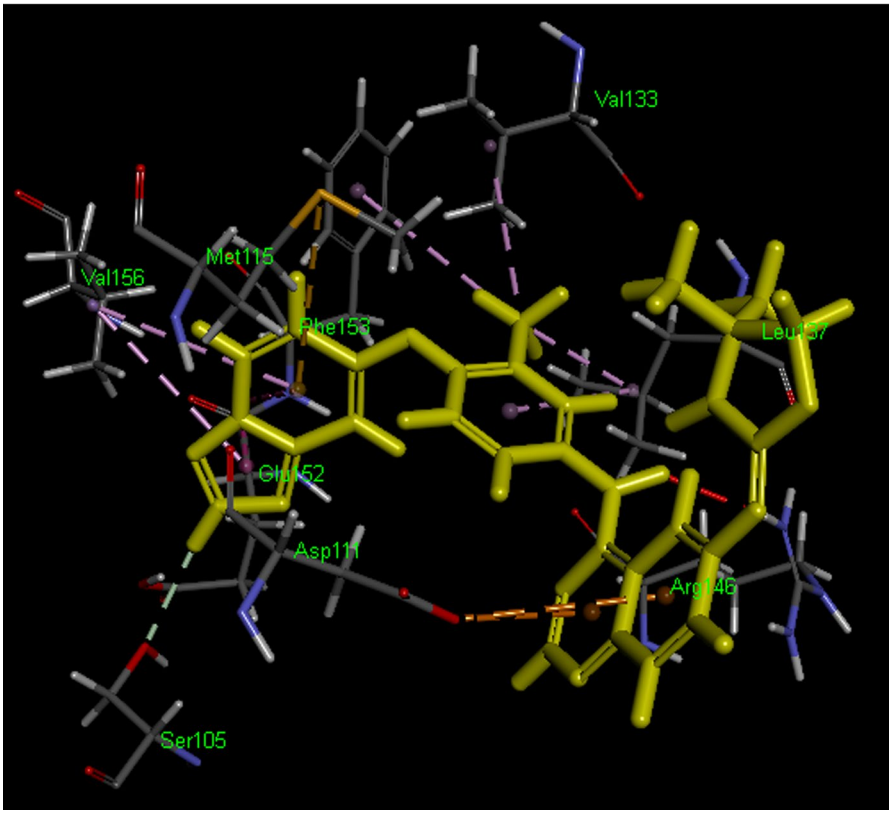

Fig. 3 Non-bonded interactions of the highest scoring pose of *Tucatinib* (LibDock score: 54.80—low score) of *Bcl-2* target protein (PDB id: 6QGH)

the compounds considered for the present study) LibDock score while Tucatinib has failed to achieve that.

3.3 Lipinski's rule-of-five filtering results

In this section, we have reported the findings obtained from Lipinski's Rule-of-Five [16] filtering and some other considerations [13] for the compounds screened from the docking studies to identify the most probable potential anti-oral cancer drug molecules. To obtain these potential compounds from Tables 1 and 2 (docking results), we have investigated those compounds that possess apoptosis-related properties, as described in PubChem [13], taking into consideration the role Bcl-2 plays in apoptosis [2] which seems to be relevant in the present context. In the process, we have found nine such compounds from those shown in Table 1. Out of those nine compounds, we have found seven compounds (Compounds 1–7 in Table 6) to be most suitable in that we have considered those compounds which are already

Table 4 Details of the non-bonded interactions of the highest-scoring pose of *Tucatinib*

Serial No.	Non-bonded interaction type	Color of the bond as in Fig. 3	Non-bond between
1.	Carbon H-Bond	Light Green	51,039,094:H60 – A:SER105:OG
2.	Electrostatic (Pi-Anion)	Brown	A:ASP111:OD2–51,039,094
3.	Electrostatic (Pi-Anion)	Brown	A:ASP111:OD2–51,039,094
4.	Other (Pi-Sulfur)	Light Brown	A:MET115:SD – 51,039,094
5.	Hydrophobic (Amide-Pi stacked)	Pink	A:GLU152:C,O; PHE153:N – 51,039,094
6.	Hydrophobic (Amide-Pi stacked)	Pink	A:GLU152:C,O; PHE153:N – 51,039,094
7.	Hydrophobic (Alkyl)	Light Purple	51,039,094:C30 – A:VAL133
8.	Hydrophobic (Alkyl)	Light Purple	51,039,094:C30 – A:LEU137
9.	Hydrophobic (Pi-Alkyl)	Light Purple	A:PHE153–51,039,094:C30
10.	Hydrophobic (Pi-Alkyl)	Light Purple	51,039,094 – A:VAL156
11.	Hydrophobic (Pi-Alkyl)	Light Purple	51,039,094 – A:VAL156
12.	Hydrophobic (Pi-Alkyl)	Light Purple	51,039,094 – A:LEU137

Table 5 Details of the unfavorable non-bonded interactions of the highest scoring pose of *Tucatinib*

Serial no.	Unfavorable non-bonded interaction type	Color of the bond as in Fig. 3	Non-bond between
1.	Unfavorable	Red	A:ARG146:HH12 – 51,039,094:H38

approved by FDA or other such agencies and/or do not have any major side effects such as liver toxicity/injury [13]. Subsequently, we have identified three such compounds from Table 2 as well which have returned quite high LibDock scores; i.e., their LibDock scores are much closer to 100 compared to many other compounds docked. Moreover, these compounds are devoid of the side effects mentioned above. All the compounds shown in Table 6 have been found to satisfy Lipinski's Rule-of-Five [16]. It may be noted that in PubChem [13], the partition coefficient (logP) has been given as computed XlogP3-AA or XlogP3 values. Now, that the compounds shown in Table 6 have got high LibDock scores [15] and satisfy Lipinski's Rule-of-Five [16], these compounds may be regarded as the most probable potential anti-oral cancer drug molecules obtained from the present study.

Table 6 Identified most probable 10 potential anti-oral cancer drugs

Serial No.	Compound name	PubChem CID	LibDock score
1.	Olaparib	23,725,625	124.36
2.	Seliciclib	160,355	116.36
3.	Amrubicin	3,035,016	103.66
4.	Filanesib	44,224,257	102.98
5.	Panobinostat	6,918,837	102.40
6.	Artesunate	60,196,289	100.84
7.	Cephalotaxine	278,679	100.10
8.	Entinostat	4261	98.99
9.	Vorinostat	5311	95.12
10.	Lenalidomide	216,326	91.12

4 Conclusion

The purpose of the present study is to identify potential anti-oral cancer drug molecules from known anti-neoplastic agents, a particularly important class of compounds, through small molecule docking studies and Ripinski's Rule-of-Five filtering. This is believed to help identify potential anti-oral cancer drugs as these compounds already show anti-neoplastic properties. For example, Olaparib, the most probable potential anti-oral cancer drug, identified from the present study, works by taking advantage of a defect in Deoxyribonucleic Acid (DNA) repair in cancer cells with BRCA (breast cancer gene) mutation and inducing cell death [13]. Moreover, Olaparib is a drug in use for the treatment of various cancers like ovarian cancer, breast cancer, pancreatic cancer, and prostate cancer [13]. All these seem to indicate that the identification of Olaparib as a potential anti-oral cancer drug is reasonable. Another important role that a Bcl-2 inhibitor can play is to control the over-expression of Bcl-2 which may confer resistance to chemotherapeutic drug treatment e.g., resistance of oral tongue squamous cell carcinoma (OTSCC) cells to cisplatin [9]. Therefore, the identification of effective Bcl-2 inhibitors is important, and the present approach is believed to find useful applications in this regard. Furthermore, it would be interesting to see by carrying out experimental work e.g., through studies on a cell line (in vitro) of interest, whether the identified compounds are able to exhibit anti oral-cancer activity, alone or in combination with other anti-oral cancer drugs.

Finally, the results obtained from these studies seem to be encouraging in identifying the most probable potential anti-oral cancer drugs as apparent from the docked poses shown in Figs. 1, 2, 3 and 4 for comparative analyses. While we have identified the 10 most probable potential anti-oral cancer drug molecules, one can always consider other compounds of one's interest from those given in Tables 1 and 2. It appears that the findings of the present study and the approach followed in this purpose may significantly help discover anti-oral cancer drugs as Bcl-2 inhibitors for the protein target considered here and possibly for other relevant receptor targets as well by screening known anti-neoplastic agents.

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Author contributions CR did analysis, drafted the paper; SS performed analysis; DP reviewed the draft and finalized the manuscript. All authors reviewed the manuscript and approved the same.

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Declarations

Competing interests There is no conflict of interest among the authors. All the authors have contributed to doing the work and writing the manuscript.

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