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QSAR and Docking Studies of Pubchem Derivatives as Potential Alk Inhibitors for Non-Small Cell Lung Cancer

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ABSTRACT

Crizotinib is an anticancer drug used for the treatment of non-small cell lung cancer. The emergence of several mutations in the ALK gene suppresses the crizotinib action. It is then required to develop potent anti-cancer drugs for the treatment of crizotinib resistance, non-small cell lung cancer types. In the present study, a novel class of lead molecules was identified using QSAR analysis, bioavailability analysis and molecular docking studies. QSAR analysis was performed with the help of HyperChem software and bioavailability analysis was carried out using Molinspiration program. Patch Dock Server was employed for the docking studies to find out the binding affinity of lead compounds with the target protein. Our analysis clearly indicates that CID 11562217 and CID 11562021 molecules, pyrazole-substituted aminoheteroaryl compounds, could be the prospective ALK inhibitors undoubtedly useful to overcome the drug resistance in non-small cell lung cancer.

Keywords: ALK; Crizotinib; Docking; NSCLC; HyperChem; QSAR

INTRODUCTION

Cancer is a standout amongst the most destroying maladies on the planet and just an unobtrusive change has been found in the time of the most recent five years with the assistance of 'better than ever' treatments. It has been seen one out of each four death are due to cancer and the vast majority of them who are determined to have the ailment figure out to get it for further five years. Lung cancer is in charge of the biggest number of deaths around the world [1]. In India, lung growth comprises 6.9% of all new cancer reports and 9.3% of all cancer deaths. Lung tumours are extensively classified into two primary sorts based upon their histology, which are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The most widely recognized types of NSCLC are adenocarcinoma (ADC) and squamous cell carcinoma (SCC) with NSCLC represents around 85-90% of all lung malignancies [2]. Crizotinib was approved by the U.S. Food and Drug Administration (FDA) under the trade name Xalkori for the management of advanced fusion-type NSCLC in 2011 merely after four years of clinical experiments [3]. Crizotinib take actions against ALK through mechanism of ATP competitive kinase inhibitor, anticipating binding of ATP and ensuing autophosphorylation, which is needed for launching of the enzyme. The high feedback proportion made crizotinib as a standout amongst the best medications for the treatment of lung malignancy. Be that as it may, inevitably cancer cells created resistance. This take place as the tumor cells step by step created change in them against the medication, along these lines making the medication insufficient against the cancer. The experimental evidences indicate that ALK mutation such as C1156Y confer higher level of resistance to crizotinib among the patients [4, 5]. C1156Y ALK mutation is located in the N terminal to the Cα-helix within the kinase domain. Mutation in the ALK will lead to drug resistance, thereby decreasing the drug efficacy of crizotinib. Most importantly, the available evidence indicates that ALK mutation (C1156Y) is one of the main causes for crizotinib resistance [6, 7]. These situations drive the development of new and more effective ALK inhibitors especially for the treatment of drug resistance NSCLC [8, 9]. Therefore, in the present investigation, we have employed QSAR and docking studies to address the crizotinib resistance in NSCLC. QSAR properties of lead compounds were executed with HyperChem software [10]. Quantitative structure activity relationships (QSARs) are generally utilised in the drug design process where the experimental information about ligand–receptor interactions is not available. Further, the molinspiration tool was used to

evaluate bioavailability of lead compounds [11]. Finally, molecular docking program was employed using Patch Dock to find out the binding affinity of lead compounds with the target protein [12]. The outcomes are of incredible significance for the revelation of better therapeutic molecules atoms to counter the existing drug resistance.

EXPERIMENTAL SECTION

Dataset: The three-dimensional (3D) structure of native and mutant (C1156Y) ALK structure was obtained from the crystal structures of the Brookhaven Protein Data Bank (PDB) [13]. The corresponding PDB codes were 2XP2 and 2YJS for the native and mutant structures respectively [14]. The small molecule used in our study was crizotinib. The SMILES strings of the crizotinib and the lead molecules were collected from PubChem [15, 16]. For the construction of 3D structure of molecule, the molecules were submitted to CORINA server [17]. The present study initiated by extracting structurally similar compounds to crizotinib from the PubChem database. It is important to note that the PubChem database contains 54 million entries of pure and characterized chemicals and is a freely available database maintained by NCBI. Several hits were obtained from the PubChem database and about 95% similarity cut-off was maintained in the analysis.

QSAR and molecular properties: QSAR properties of crizotinib and lead compounds were obtained using HyperChem 8.0 software [18]. With the help of HyperChem software several properties can be studied together. The bioavailability of the lead compounds was examined with the assistance of Lipinski's rule of five. The rule states that most molecules with good membrane permeability should have a molecular weight ≤ 500, calculated octanol–water partition coefficient, log P ≤ 5, hydrogen bond donors ≤ 5, acceptors ≤ 10 and van der Waals bumps polar surface area (PSA) <120 $Å^2$ [19, 20]. Molinspiration, an online tool was used to calculate molecular properties such as TPSA, nON, nOHNH and nrotb (http://www.molinspiration.com/cgi-bin/properties).

Molecular Docking: The docking study is immensely important to understand the bioactivity of the screened lead compounds. Patch Dock calculation was used to perform docking investigation. It is a molecular docking algorithm based on shape complementarily principles. The PDB coordinate record for the protein and the ligand particle are the data parameters for the docking. This calculation has three noteworthy stages (i) Molecular Shape Representation (ii) Surface Patch coordinating and (iii) Filtering and Scoring [12]. This administration of Patch Dock was accessible at http://bioinfo3d.cs.tau.ac.il/PatchDock. The docked complexes were ranked based on the geometric matching score with target proteins (2XP2 and 2YJS) and were used as reference for filtering the lead compounds.

RESULTS AND DISCUSSION

Calculation of QSAR properties using HyperChem

The 3-D structures of native and mutant structure were obtained from RCSB protein data bank (Fig. 1) and a total of 59 compounds were considered in our study for screening ALK inhibitor from the PubChem database.

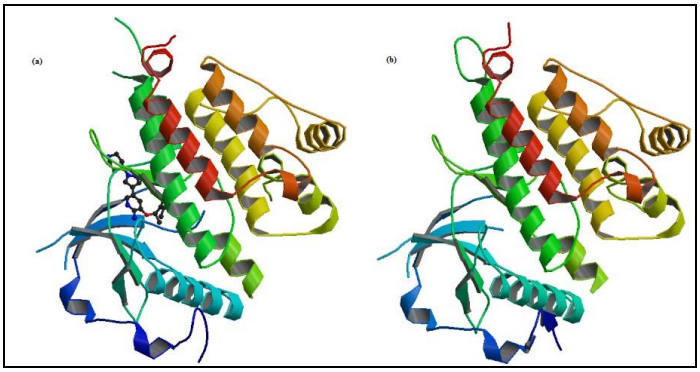

Figure 1: 3-D structure obtained from RCSB protein data bank (a) native (PDB Code 2XP2) and (b) mutant (PDB Code 2YJS)

Initial screening was accomplished by calculating molecular properties using HyperChem software 8.0.10 for windows. QSAR properties such as log P, surface area, mass, molar refractivity, polariziability and volume were calculated. The properties of crizotinib were used as a control for screening the other lead compounds. The result is shown in Table1. logP is a measure for compound's hydrophobicity and an important parameter for drug likeliness. The high logP value indicates that compounds retention will be less into the intestines because of the low hydrophobicity. The desired log P value should not be more than 5.0 [19]. It is clear from the table1 that almost all the 60 compounds showed log P values less than 5.0. Transport characteristics of drug molecule

such as intestinal absorption or blood-brain barrier penetration depend on molecular volume. Therefore, volume is subsequently utilized as a part of QSAR studies to model biological activity and molecular properties. For the better absorption, the molecular mass should be under 500 DA/amu. The molecular weight of crizotinib was found to be 450.34 amu. In the table 1, twenty three compounds showed same molecular mass as that of crizotinib whereas all other remaining compounds showed molecular mass less than 500 amu. Polarizability is the capacity of the electrons to react to a changing electric field and this parameter checks van der waals interactions and non bonded interactions [21]. Molecules having high polarizability are known to have strong attractions with other molecules and can also enhance aqueous solubility. Generally, the polarizability values are in accord with the values of surface area, molecular volume and refractivity values. Molar refractivity is also related with london dispersive forces (loose van der Waals forces) that plays an important role in protein drug interaction. In our dataset, the polarizability values range from 37.47 A^3 to 59.86 A^3 whereas the molar refractivity values range from 39.92 A^3 to 71.99 A^3. Surface area (Approx.) values range from 485.76 A^2 to 630.86 A^2 and surface area (Grid) values range from 562.38 A^2 to 717.41 A^2 for the compounds analysed in our study. For instance, QSAR properties of CID11562217 molecule analyzed with the help of HyperChem software (Fig. 2). Further properties such as TPSA, nON, nOHNH, nrotb of crizotinib and lead compounds were evaluated with the help of molinspiration.

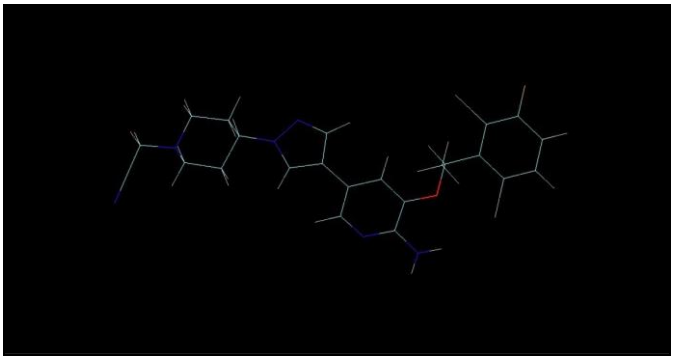

Figure 2: QSAR properties of CID11562217 molecule analyzed with the help of HyperChem software

Bioavailability analysis

The bioavailability analysis was carried out with the Molinspiration program. Crizotinib properties were calculated (Figure 3) and used as a control for screening the other lead compounds.

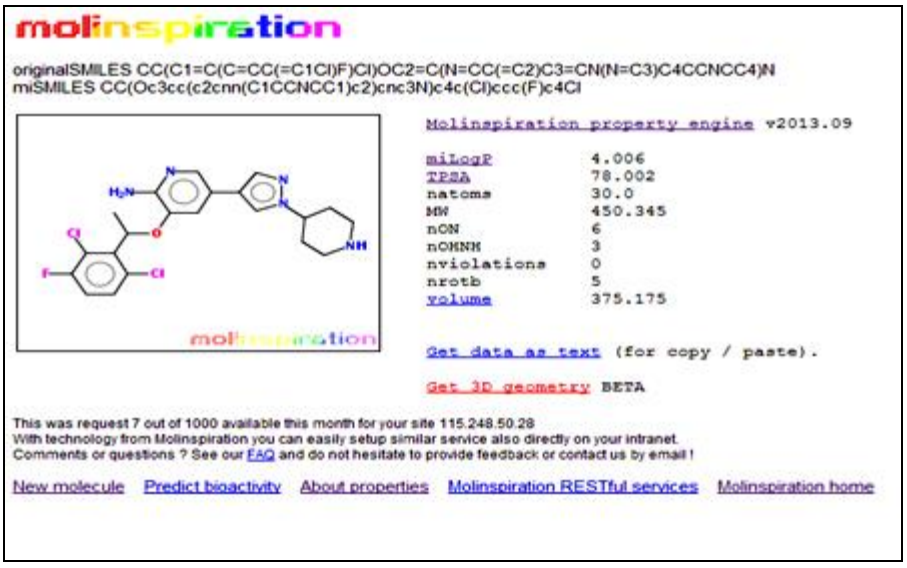

Figure 3: Molinspiration property explorer showing molecular properties of crizotinib

TPSA (Total polar surface area) is an exceptionally valuable parameter for prediction of drug transport properties

Table 1: QSAR Properties of crizotinib and lead compounds obtained using Hyperchem 8.0 software

S. No.	Compound	log P	Surface Area (Approx) (A2)	Surface Area (Grid) (A2)	Mass (amu)	Molar Refractivity (A3)	Polariziability (A3)	Volume (A3)
1	Crizotinib	2.43	546.66	661.96	450.34	60.08	45.38	1149.28
2	11719356	2.79	594.66	686.33	464.37	65.37	47.22	1197.44
3	11496366	2.83	549.83	666.67	450.34	59.86	45.38	1162.86
4	11503318	2.83	549.83	666.67	450.34	59.86	45.38	1162.86
5	11510387	2.38	522.53	641.49	436.32	55.21	43.55	1103.26
6	11562021	2.79	594.66	686.33	464.37	65.37	47.22	1197.44
7	11562217	2.85	630.86	715.26	489.38	71.04	49.07	1250.36
8	11568619	2.83	549.83	666.67	450.34	59.86	45.38	1162.86
9	11575401	2.33	505.18	620.68	422.29	50.35	41.71	1061.48
10	11597571	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
11	11612136	2.65	542.08	654.28	451.33	58.4	44.67	1136.06
12	11625675	3.57	540.14	615.26	409.29	49.09	41.14	1054.59
13	11626560	2.43	546.66	661.96	450.34	60.08	45.38	1149.28
14	11626823	2.85	576.7	685.19	464.37	64.9	47.22	1198.95
15	11626824	2.79	594.66	686.33	464.37	65.37	47.22	1197.44
16	11641497	2.24	620.93	717.41	479.38	68.7	48.57	1245.19
17	11647759	2.35	541.64	648.41	436.32	55.24	43.55	1197.44
18	11647760	2.38	522.53	641.49	436.32	55.21	43.55	1103.26
19	11647795	2.6	514.43	629.37	473.3	53.53	42.84	1089.82
20	11662380	2.83	541.62	661.69	450.34	59.86	45.38	1146.96
21	11676140	3.61	500.57	623.34	421.3	51.73	42.2	1070.48
22	11676204	2.43	582.43	646.96	424.31	52.65	42.49	1105.5
23	11684380	3.22	624.52	711.26	478.4	70.19	49.05	1248.93
24	11690598	2.05	533.4	659.94	433.89	55.49	43.37	1129.19
25	11705849	3.26	516.52	681.89	490.41	72.25	50.12	1209.3
26	21110753	2.45	617	709.16	480.37	67.02	47.86	1232.89
27	21110757	2.82	485.76	562.38	381.24	39.92	37.47	958.84
28	44560358	2.02	548.95	661.39	436.32	55.66	43.55	1127.69
29	53234260	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
30	53234326	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
31	54613769	2.43	549.62	664.71	450.34	60.08	45.38	1149.39
32	56671814	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
33	58659130	2.05	549.76	653.26	433.89	55.49	43.37	1129.95
34	58659136	2.38	522.53	641.49	436.32	55.21	43.55	1103.26
35	58659141	3.61	500.57	623.34	421.3	51.73	42.2	1070.48
36	58659189	2.5	573.17	682.88	446.38	64.78	47.31	1186.07
37	58659191	2.68	558.62	663.28	468.33	59.98	45.29	1157.08
38	58659192	3.15	486.78	666.89	494.37	66.87	48.19	1169.99
39	59599446	1.72	567.81	690.16	480.37	66.26	47.86	1206.91
40	60197531	2.43	546.67	661.96	450.34	60.08	45.38	1148.58
41	60197626	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
42	60198523	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
43	60198524	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
44	60198525	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
45	60199015	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
46	60199016	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
47	60199073	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
48	60199075	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
49	60199076	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
50	60199077	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
51	62705017	2.43	546.72	660.23	450.34	60.08	45.38	1148.19
52	67084493	2.74	509.66	687.54	476.38	67.3	48.28	1186.39
53	68563708	2.05	533.4	657.94	433.89	55.49	43.37	1129.19
54	68625002	3.27	593	698.47	478.4	69.31	49.05	1235.05
55	71239831	3.34	581.41	715.25	490.41	71.83	50.12	1253.48
56	71239833	3.34	581.41	715.25	490.41	71.83	50.12	1253.48
57	71240010	3.2	582.92	713.67	490.41	71.99	50.12	1255.36
58	71240011	3.2	582.92	713.67	490.41	71.99	50.12	1255.36
59	72986690	2.83	549.83	666.67	450.34	45.38	59.86	1162.86
60	73386634	2.82	485.76	562.38	381.24	39.92	37.47	958.84

Table 2: Calculation of molecular properties (TPSA, nON, nOHNH, nrotb) of crizotinib and lead compounds using molinspiration

S. No.	Compound	TPSA	nON	nOHNH	Nrotb
1	Crizotinib	78.002	6	3	5
2	11719356	78.002	6	3	5
3	11496366	69.213	6	2	5
4	11503318	78.002	6	3	6
5	11510387	78.002	6	3	5
6	11562021	69.213	6	2	6
7	11562217	93.005	7	2	5
8	11568619	78.002	6	3	6
9	11575401	78.002	6	3	5
10	11597571	78.002	6	3	5
11	11612136	75.209	6	2	5
12	11625675	65.975	6	2	5
13	11626560	78.002	6	3	5
14	11626823	78.002	6	3	6
15	11626824	69.213	6	2	5
16	11641497	69.213	6	2	5
17	11647759	78.002	6	2	6
18	11647760	78.002	6	3	5
19	11647795	75.209	6	2	5
20	11662380	78.002	6	2	5
21	11676140	65.975	5	2	5
22	11676204	78.002	6	3	7
23	11684380	69.213	6	3	6
24	11690598	78.002	6	3	5
25	11705849	69.213	6	2	5
26	21110753	78.447	7	2	7
27	21110757	65.975	5	2	4
28	44560358	78.002	6	3	5
29	53234260	78.002	6	3	5
30	53234326	78.002	6	3	5
31	54613769	78.002	6	3	5
32	56671814	78.002	6	3	5
33	58659130	78.002	6	3	5
34	58659136	78.002	6	3	5
35	58659141	75.209	6	2	6
36	58659189	78.002	6	3	5
37	58659191	78.002	6	3	5
38	58659192	78.002	6	3	5
39	59599446	98.23	7	4	6
40	60197531	78.002	6	3	5
41	60197626	78.002	6	3	5
42	60198523	78.002	6	3	5
43	60198524	78.002	6	3	5
44	60198525	78.002	6	3	5
45	60199015	78.002	6	3	5
46	60199016	78.002	6	3	5
47	60199073	78.002	6	3	5
48	60199075	78.002	6	3	5
49	60199076	78.002	6	3	5
50	60199077	78.002	6	3	5
51	62705017	78.002	6	3	5
52	67084493	78.002	6	3	6
53	68563708	78.002	6	3	5
54	68625002	78.002	6	3	6
55	71239831	78.002	6	3	5
56	71239833	78.002	6	3	5
57	71240010	78.002	6	3	5
58	71240011	78.002	6	3	5
59	72986690	78.002	6	3	6
60	73386634	65.975	5	2	4

Polar surface area is described as a sum of surfaces of polar atoms (usually oxygens, nitrogens and attached hydrogens) in a molecule and this parameter has been appeared to connect extremely well with drug absorption, including blood–brain barrier penetration, bioavailability, $CaCO_2$, intestinal absorption and permeability. nrotb (number of rotatable bonds) is a topological parameter and it measures molecular flexibility.
Molecular flexibility plays a crucial role in drug design and nrotb has been appeared to be a decent descriptor of oral bioavailability of drugs. In the present study, molecular properties for all the lead compounds were in accordance with Lipinski rule of five. The reference value used in molinspiration for polar surface area (PSA) should be <120 $Å^2$ [22] and for number of rotatable bonds (nrotb), the value should be less than 10 [23]. The result is presented in table 2. It is clear from the table 2 that almost all the 60 compounds screened possess polar surface area (<120 $Å^2$) and reasonable number of rotatable bonds (<10). All the molecules used in our study showed zero violations for the rule of five. The result indicates that these compounds may have the potential to become a lead compound. Finally docking analysis was carried out to screen the potent lead compounds.

Table 3: Docking score of the crizotinib and lead compounds obtained from PubChem database against the target structure

S.no.	Compound id	Score		S.no.	Compound id	Score	
		2XP2	2YJS			2XP2	2YJS
1	Crizotinib	5042	4918	31	54613769	5298	4888
2	11719356	5040	4936	32	56671814	5312	4918
3	11496366	5412	5190	33	58659130	5108	4892
4	11503318	5110	5006	34	58659136	5124	4770
5	11510387	5124	4770	35	58659141	5118	4614
6	11562021	5510	5190	36	58659189	5116	4874
7	11562217	5662	5360	37	58659191	5320	5028
8	11568619	5110	5006	38	58659192	5470	4876
9	11575401	4886	4648	39	59599446	5434	5106
10	11597571	5312	4918	40	60197531	5312	4910
11	11612136	5144	4866	41	60197626	5312	4918
12	11625675	4746	4794	42	60198523	5312	4918
13	11626560	5312	4728	43	60198524	5312	4918
14	11684380	4964	4938	44	60198525	5312	4918
15	11626824	5412	5190	45	60199015	5312	4918
16	11641497	5450	5120	46	60199016	5312	4918
17	11647759	5026	4950	47	60199073	5312	4918
18	11647760	5124	4770	48	60199075	5312	4918
19	11647795	5268	4604	49	60199076	5312	4918
20	11662380	4906	4744	50	60199077	5312	4918
21	11676140	4906	4614	51	62705017	5312	4918
22	11676204	4964	4768	52	67084493	4950	4662
23	11684380	4964	4938	53	68563708	4906	4862
24	11690598	4906	4862	54	68625002	5200	5056
25	11705849	5186	5368	55	71239831	5400	5284
26	21110753	5390	5384	56	71239833	5400	5284
27	21110757	4408	4364	57	71240010	5426	5414
28	44560358	5012	4884	58	71240011	5426	5414
29	53234260	5312	4918	59	72986690	5110	5006
30	53234326	5312	4918	60	73386634	4408	4364

Molecular docking analysis
Molecular docking program was employed to find out the binding affinity of lead compounds with the target protein. Docking analysis was performed twice to eliminate the false positive. The docking results are shown in table 3. The docking score of native-type ALK-crizotinib complex was found to be 5042 and for the mutant-type ALK-crizotinib complex was found to be 4918. The lesser docking score of mutant complex clearly designates that mutation (C1156Y) significantly affects the binding of crizotinib with the ALK structure. It is believed that a potential lead compound is the one should have higher docking scoring than the existing drug molecule, crizotinib. Therefore, we have examined docking score for all the 59 hits both with the native type and with the mutant type ALK (Table 3). 15 hits in the mutant structure showed similar dock score as that of 2YJS-crizotinib complex. 44 hits showed higher docking score only with 2XP2-crizotinib complex. Most importantly, 17 hits from our dataset showed higher dock score both in the native type (2XP2) as well as with mutant type (2YJS) ALK-crizotinib complex. For instance, CID 11562217 and CID 11562021 molecules showed the highest docking score among the 17 hits in our data set. The docking score of 2XP2-CID 11562217 complex was found to be 5662 whereas for the 2YJS-CID 11562217 complex was found to be 5360 and for the 2XP2-CID 11562021 complex, the score was found to be 5510 whereas for the 2YJS-CID 11562021 complex, the score was found to be 5190. This result indicates that these molecules have a better

binding affinity not only with the native type but also with mutant ALK as compared to the crizotinib. The two dimensional structure of crizotinib was evaluated with CID 11562217 and CID 11562021 to get the structural attributes and the result is demonstrated in Fig. 4. The literature evidence also highlights that our lead molecules have kinase inhibiting effects (US Patent 20060128724) and possess anti-cancer activity [24].

Bold indicates the lead compounds showed higher binding score than crizotinib.

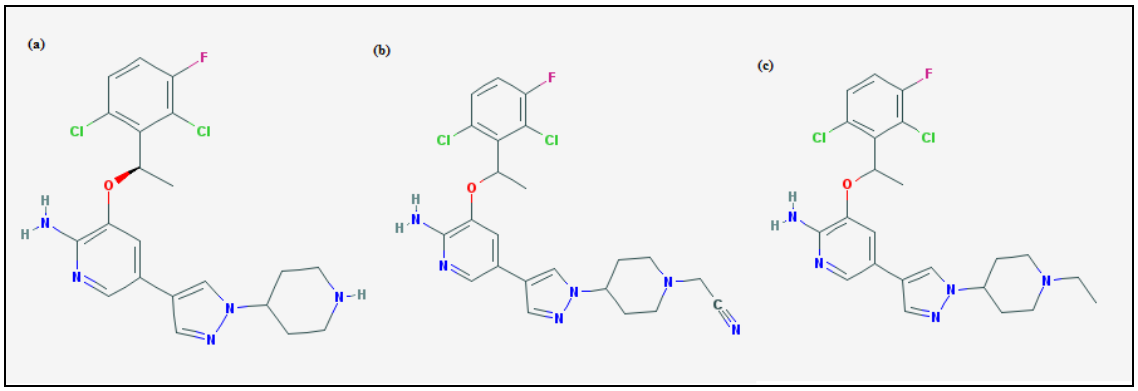

Figure 4: Structure comparison between (a) crizotinib (b) CID11562217 and (c) CID 11562021 obtained from the PubChem database

CONCLUSION

In this study, we have dealt with the crizotinib resistance in NSCLC with the help of QSAR and docking studies. Overall, CID 11562217 and CID 11562021 showed good QSAR properties when compared with the other molecules. Further, these compounds showed zero violations according to the rule of five. Finally, docking studies showed that CID 11562217 and CID 11562021 have the highest binding affinities not only with native type ALK but also with the mutant type ALK (C1156Y) among the lead compounds considered in our study. Experimental evidences also suggest that pyrazole-substituted aminoheteroaryl compounds act as protein kinase inhibitors and are useful in the treatment of abnormal cell growth disorders, such as cancers. We hope that the findings reported here might give supportive signs to devise powerful drugs against drug resistant lung cancer types.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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