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Research Article

PREDICTION OF CYANOBACTERIAL DRUG FOR BLOOD CANCER THROUGH MOLECULAR DOCKING

Sangeetha M[1*]., Menakha M[2] and Vijaya Kumar S[3]

[1]Department of Microbiology, Kamaraj College, Tuticorin, Tamil Nadu-India
[2]Department of Biotechnology, MASS College of Arts and Science Kumbakonam
[3]Department of Botany and Microbiology, A.V.V.M.Sri Pushpam College, Poondi, Thanjavur, Tamil Nadu-India

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A B S T R A C T

The aim of the present study was to predict the interaction between selected cyanobacterial bioactive compounds and blood cancer causing target protein. The blood cancer causing target protein, BCR-ABL tyrosine kinase protein structure was selected and used to check the susceptibility with selected cyanobacterial bioactive compounds. The extent of interaction of the selected cyanobacterial bioactive compounds with a target protein was predicted using *in silico* molecular docking studies. Among the selected cyanobacterial bioactive compounds, Lyngbyabellin D1 was found to be effective and interacted strongly with selected blood cancer causing target protein. The results of the study support the fact that *in silico* molecular docking studies are very useful in predicting the blood cancer curing drug from cyanobacterial bioactive compounds.

INTRODUCTION

Marine cyanobacteria are the most promising organism with potential benefits against cancer. Among marine cyanobacteria, the genus *Lyngbya* is considered to be the most prolific producer of natural products with over 200 compounds reported. *Lyngbya majuscula* (Lyngbya) is a naturally occurring, thread-like, marine cyanobacterium. Bioactive compounds from *Lyngbya* are considered to be a valuable pool of lead compounds in structure-based drug design and discovery [1]. Several compounds were found to inhibit the growth of cancer cell lines. Many of these compounds are bioactive and show potential for therapeutic use. The genus Lyngbya appears to be an emerging source of bioactive peptides. Several of the lyngbyabellins are reported to exhibit moderate to potent cytotoxicity to various cancer cell lines and to exert this activity through interference with the actin system. Lyngbyabellin was derived from the marine cyanobacterium *Lyngbya majuscula*. It exhibited attractive cytotoxic properties against the human cancer cell lines and were shown to be potent disrupters of the cellular microfilament network [2]. Cancer treatments do not have potent medicine as the currently available drugs are causing side effects in some instances [3]. The side effects of the commercially available drugs make the need for the necessity of new improved drugs and hence, in this investigation a new drug from cyanobacterial origin has been tried showing high binding affinity with the receptor molecule of blood cancer.

Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to, in turn, predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs [4]. Therefore docking is useful for predicting the strength and binding nature of the receptor and ligand molecules [5]. The focus of molecular docking is to computationally simulate the molecular recognition process. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized.

MATERIALS AND METHODS

Blood cancer causing BCR-ABL tyrosine kinase protein structure was retrieved from protein databank [6] and the marine cyanobacterial bioactive compounds molecular structures were retrieved from Chemspider database [7]. The docking tool Glide was used for molecular docking [8]. In the present study with the help of Glide, Maestro, LigPrep and SiteMap were used to locate binding sites over the protein molecule and to conduct molecular docking of ligands with the protein molecules.

Corresponding author:* **Sangeetha M
Department of Microbiology, Kamaraj College, Tuticorin, Tamil Nadu-India

RESULTS AND DISSCUSSION

Molecular Docking of Bcr-Abl Tyrosine Kinase Protein With Bioactive Compounds of Cyanobacteria

Molecular docking was performed between the BCR-ABL tyrosine kinase protein (Fig.1) of blood cancer with bioactive compounds of cyanobacteria.

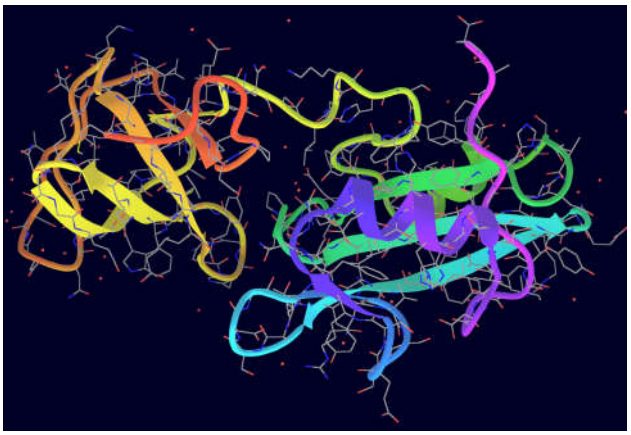

Fig 1 Structure of BCR-ABL tyrosine kinase

The 3-D structure of the BCR-ABL tyrosine kinase protein was provided with three ligand binding sites present (Table.1 & Fig.2). The bioactive compounds (Fig.3) were recognizing the first site as a major active binding active site for the molecular docking. The above target protein and ligands (bioactive compounds) were geometrically optimized. All the ligand molecules were docked against the active sites of the target protein using Glide software (Fig.4). The docking results were presented in the form of glide docking score in negative values (Table.2). In the docking studies, higher negative values represent high binding affinity between the receptor and ligand molecules, indicating the higher efficiency of the bioactive compounds.

Table 1 Site map scores of BCR-ABL tyrosine kinase protein

Sites	2ABL
Site-1	0.998798
Site-2	0.660338
Site-3	0.595385

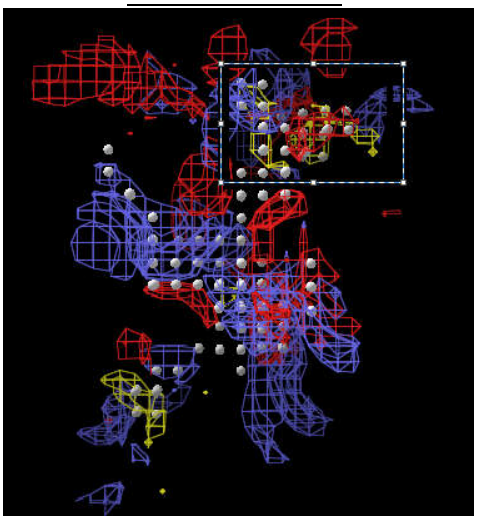

Fig 2 Active sites of BCR-ABL tyrosine kinase (Major active site present inside the box)

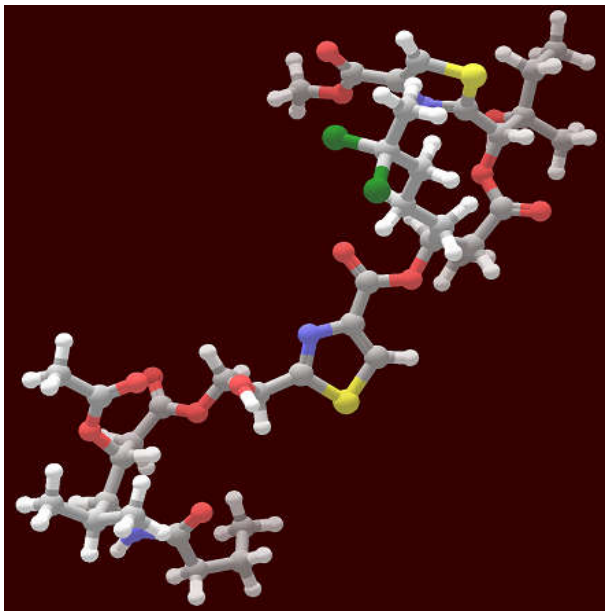

Fig 3 Structure of lyngbyabellin

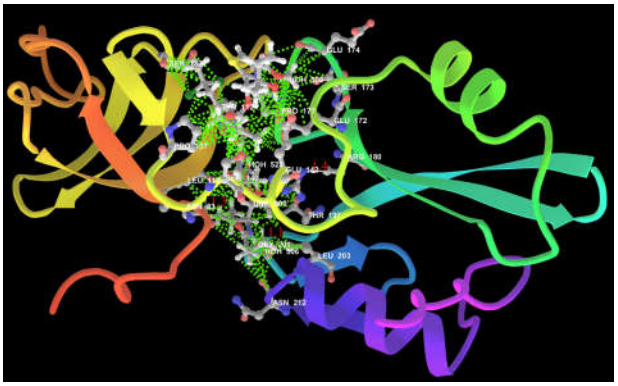

Fig 4 Molecular docking of BCR-ABL tyrosine kinase with lyngbyabellin

Table 2 Docking scores of BCR-ABL tyrosine kinase protein with lynbaybellin D1

Cyanobacterial Bioactive Compounds with Blood Cancer (2ABL)	Glide Docking Score
10479838(**lynbaybellin D1**)	**-8.74718**
8161464 (cryptopycin F)	-6.222356
10214176(nostocylopeptide A2)	-6.205213
27024729(lyngbyastatin 8)	-6.151617
28289559(hoiamide D1)	-6.131953
27023225(symplocamide A1)	-6.103508
24662743(molasamide)	-6.049267
23314421 (symplocamide A)	-6.003956
27024730(lyngbyastatin 9)	-5.987283
27024666(tiglicamide B)	-5.973412
17214383(lynbyastatin 4)	-5.949786
9290490(somocystinamide A)	-5.907581
24712280(kemopeptinde B)	-5.864238
24687950(kemopeptine A)	-5.768791
10214175(nostocyclopeptide A1)	-5.7398
28185012(hoiamide D)	-5.646199
27024665(tiglicamide A)	-5.63187
8616107(tasipeptin A)	-5.602533
25032428(hoamide C)	-5.5276
23310527 (lyngbyastatin 3)	-5.513978
8158691 (cryptopycin G)	-5.425397
26386326(malyngamide 2)	-5.416295
10193999(symplostatin 2)	-5.402874
23076612(lyngbyastatin 7)	-5.383133
9939878 (cryptopycin E)	-5.381854
25050231(2 epi lynbaysolide)	-5.377379
28285565(kemopeptide A1)	-5.327249
10235645(lynbiabellin A)	-5.2917
24747365(largazole)	-5.083279
25053060(caylobolide B)	-5.074067
10279681(dolastin13)	-5.034161
9190271(malyngamide W)	-4.982201

Table 2 Docking scores of BCR-ABL tyrosine kinase protein with lynbaybellin D1

Cyanobacterial Bioactive Compounds with Blood Cancer (2ABL)	Glide Docking Score
9190271(malyngamide W)	-4.982201
8161120 (cryptopycin 6)	-4.967713
10213156 (cryptopycin 176)	-4.963544
28283161(lynbaybellin E)	-4.952804
10479207(caylobolide A2)	-4.917977
8546898 (cryptopycin D)	-4.912226
8798779(malyngamide M)	-4.911697
9574586 (cryptopycin 226)	-4.898553
10477231(lynbyastatin 1)	-4.896334
10242627(malyngamide Q)	-4.891666
10479739(lynbyastatin 3)	-4.835717
10478338(isomaligamide B)	-4.833416
26333470(veraguamide E)	-4.814504
7993471(calothrixin B)	-4.814404
8779889 (cryptopycin 175)	-4.802808
10480304(usneoidone2)	-4.711928
8102501(calothrixin A)	-4.657956
10478984(apratoxin C1)	-4.645917
8163332(tasipeptin B)	-4.608608
27024431(hoiamide A)	-4.604513
28288392(symplostatin analogue 4)	-4.59217
9344966 (cryptopycin 326)	-4.576285
10480303(usneoidone)	-4.573428
9398012(calothrixin B2)	-4.555545
24713265(apratoxin E)	-4.552431
10229166(malyngamide V2)	-4.537158
23339539(homodolastin 16(1)	-4.535743
4579048 (cryptophycin)	-4.502834
552662 (obynanamide 1)	-4.497096
10275264(malyngamide C)	-4.488596
28289545(basilynbiyaside 1)	-4.482835
24614023(symplostatin 4)	-4.473448
552443 (maleviamide D)	-4.468355
2157(aspirin)	-4.465671
10478983(apratoxin B1)	-4.465215
8827454(homodolastin 3)	-4.464692
10343167(nostocylopeptide A3)	-4.464137
8683761 (cryptopycin 16)	-4.453609
8114359 (cryptophycin 24)	-4.400514
23339511(lynbaybellin D2)	-4.367422
23339540(dolastin16(2)	-4.355502
23152209(doll5 analogs)	-4.350803
8253417 (cryptopycin C1)	-4.347035
8874822 (cryptopycin 38)	-4.279195
10479839(dolastin16)	-4.268079
552745(lynbaysolide B)	-4.26762
9597293 (cryptopycin 327)	-4.267529
8434062 (cryptopycin C)	-4.265302
10250964(malyngamide T2)	-4.264002
4579144 (cryptophycin B)	-4.262192
10478837(somocystinamide A2)	-4.253805
26377226(lagunamide A)	-4.22202
8755848 (cryptopycin 5)	-4.22007
553050(tasiamide)	-4.198872
8160989(antillatoxin B)	-4.184573
558774(malyngamide S)	-4.150908
10476818(lynbaysolide 1)	-4.14621
10476818(lynbaysolide 2)	-4.14621
4942881 (cryptophysin 1)	-4.127101
9978149(pitipeptolide A)	-4.09793
28283391(belamide A2)	-4.093599
9257758(lynbyabellin C)	-4.081533
28289216(lagunamide C)	-4.022715
27025721(pitipeptolide D)	-4.021816
9936073(malyngamide V)	-3.980439
8201342(malyngamide H)	-3.971065
10481024(lynbaybellin H)	-3.967856
26334000(veraguamide C)	-3.966015
8230892(lynbiabellin B)	-3.955748
4925356(apratoxin B)	-3.953845
27025720(pitipeptolide C)	-3.944987
9290653(arulide)	-3.944184
10242628(malyngamide R)	-3.927906
28288249(lagunamide A1)	-3.927082
9351143(kalikotoxin)	-3.922771
10448234(isomaligamide A)	-3.898684
28287038(antillatoxin 2)	-3.826662
25053061(caylobolide A1)	-3.823644
27024731(lyngbyastatin 10)	-3.803878
26399344(veraguamide B)	-3.796301
23326375(lynbaybellin B3)	-3.793467
25059566(hoiamide B)	-3.763551
10474984(doll1(2)	-3.727487
4445239(curasin A)	-3.713523

Table 2 Docking scores of BCR-ABL tyrosine kinase protein with lynbaybellin D1

Cyanobacterial Bioactive Compounds with Blood Cancer (2ABL)	Glide Docking Score
8969774(lynbayasolide)	-3.688113
26619615(ethyltomonate A)	-3.680281
27025723(pitipeptolide F)	-3.675227
9846633(dragonamide)	-3.657468
10472230(majusculamide D)	-3.653388
27025102(palmyrolide A)	-3.6035
10469767(malyngamide A)	-3.58461
27025454(isomaligamide K)	-3.581441
558793(malyngamide T)	-3.580663
10481263(arulide B)	-3.573601
8703580(malyngamide N)	-3.56278
10478302(lynbaybellin B2)	-3.554479
4885482(apratoxin A)	-3.548913
9874655(lybbaybellin G)	-3.536489
552817(malyngamide U)	-3.535905
5256890(apratoxin C)	-3.527298
4470923 (caulerpenye)	-3.515459
4470923 (caulerpenyne)	-3.515459
9489784(caulerpenye2)	-3.515459
9609508(wewakpeptin D)	-3.500746
27025519(veraguamide L)	-3.498697
10479339(lynbaysolide B1)	-3.489179
2281401(pitipeptolide B1)	-3.484237
9150045(ulongapeptin)	-3.474165
8989045(malyngamide P)	-3.466361
8920481(pseudo-dysidenine)	-3.449764
10478787 (symplostatin analogue 3)	-3.414525
10366278(arulide 1)	-3.392486
24675719(malyngolide dimmer)	-3.37053
27026161(pitiprolamide)	-3.35809
10476533(arulide3)	-3.309996
10471166(majusculamide B)	-3.304929
10147661(obynanaide 2)	-3.292311
552449(hectclorin)	-3.282452
8204655(antillatoxin 1)	-3.272053
28283201(apratoxin A1)	-3.270976
25049705(hoiamide A1)	-3.265089
8994485(pitipeptolide B)	-3.246145
10285153(malyngamide L)	-3.236905
10258245(homodolastatin 16)	-3.225321
8203335(malyngamide O)	-3.218973
8727770(malyngamide O2)	-3.218973
10481264(arulide C)	-3.214396
28286119(apratoxin A2)	-3.207416
26398953(veraguamide D)	-3.182747
10481023(lybayebellin G1)	-3.18136
9595602(antillatoxin 3)	-3.172412
424279(lybyabellin B1)	-3.168604
27025722(pitipeptolide E)	-3.165881
25050783(lynbaybellin J)	-3.153406
26333570(veraguamide G)	-3.140814
10476287(arulide2)	-3.079251
26377986(lagunamide B)	-3.066896
26341345(veraguamide A)	-2.998509
10192810(dolastin19)	-2.978337
10471165(majusculamide A)	-2.924996
23314530(majusculamide C2)	-2.915967
9960075(antillatoxin 4)	-2.906191
26398764(veraguamide F)	-2.842005
24667037(palmyramide A)	-2.809626
24707726(apatoxin D)	-2.775164
8871558(malyngamide I)	-2.76911
8227389(antillatoxin)	-2.750673
27024257(alotamide)	-2.732959
9598105(wewakpeptin B)	-2.72966
28286513(basilynbiyaside)	-2.702858
17214379(obynanamide)	-2.666571
28288461(pitiprolamide 1)	-2.502958
10477213(symplostatin analogue 1)	-2.445497
9518611(wewakpeptin C)	-2.317996
9437325 (cryptopycin 338)	-2.302711
9982437(2-epi-malyngolide)	-2.046052
137119(malyngolide)	-2.011684
10481310(belamide A)	-1.811887
28283179(malyngolide 1)	-1.614983

The recognition and affinity of ligands towards BCR-ABL tyrosine kinase protein was interpreted from the inter atomic distances and hydrogen bonding formed between the amino acid residues of docked protein-ligand complex structure. The prominent binding pockets and cavities in BCR-ABL tyrosine

kinase protein were identified using Glide module. Glide is commercial software used for docking and to predict the binding and active sites of BCR-ABL tyrosine kinase protein. To estimate the effectiveness of the cyanobacterial drug, docking between Lyngbyabellin D1 and BCR-ABL tyrosine kinase protein was conducted. In this study Lyngbyabellin D1 showed very good response with blood cancer causing protein (Table.2).

Docking of BCR-ABL tyrosine kinase protein with 191 selected bioactive ligands was carried out and the docking scores and interaction characteristics were tabulated (Table.2). Out of 191 ligands, Lyngbyabellin D1 showed a highest Glide score of -8.74718 with 3 hydrogen bonds formed between the ligand and the amino acid residues. During docking, Lyngbyabellin D1 showed three hydrogen bonding between the ligand molecule and the amino acid residues of the receptor showing a perfect binding (Fig.5). Among the 191 bioactive compounds, Lyngbyabellin D1 was identified as the most suitable drug for blood cancer.

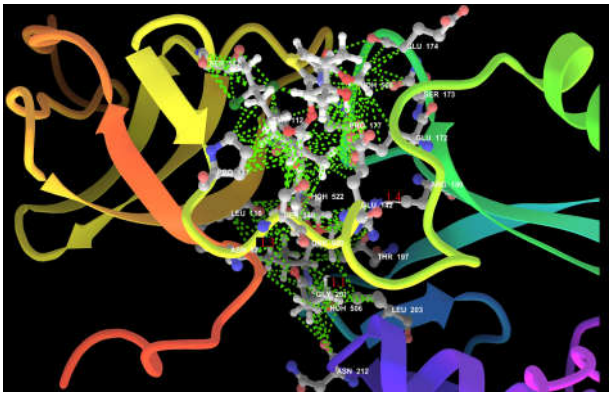

Fig 5 Molecular interaction between protein active site with ligand molecules

In the BCR-ABL tyrosine kinase protein, out of three ligand binding sites, site 1 (score 0.998798), was identified as the major active site for docking. The binding site score were ranging from 0.595385 to 0.998798. The pocket of the active site was surrounded by 33 amino acids.

The interaction of BCR-ABL tyrosine kinase protein amino acid sequence with Lyngbyabellin D1 at inter atomic distance less than 5 Å showed that the interactions between the protein and ligand had occurred only in the active site pockets of blood cancer. The high affinity of the BCR-ABL tyrosine kinase protein towards Lyngbyabellin D1 was favored by three hydrogen bonds, formed by Gly 201, Asn 83 and Glu 142 with ligand molecule Lyngbyabellin D1. The distance of the H-bonds between the above amino acids and the ligand molecules was 1.1 and 1.4 Å (Table.3 & Fig.5).

Table 3 H-bond interaction between active site amino acid residues with ligand molecules

Amino acid residues interacted ligand molecule	Distance
GLY 201-H	1.1
GLU 142- OH	1.4
ASN 83 –OH	1.3

This active binding site was lined with 33 amino acids from which 13 of them were hydrophobic, 3 were charged negative, 10 were polar, 5 were glycine and one was charged positive with n-cation (Fig.6). Therefore in this docking van der Waals forces play an important role in stabilizing the protein-ligand complex which caused higher docking score over other ligands.

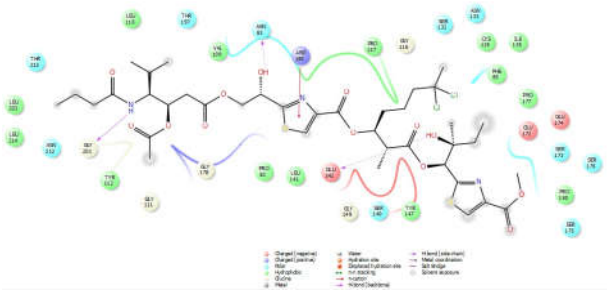

Fig 6 Ligand interaction with active site amino acid residues of BCR-ABL tyrosine kinase

The docking study reveals that van der Waals forces play an important role in stabilizing the protein-ligand complex. The van der Waals interaction and hydrogen bonding formed by the reactive amino acid residues of BCR-ABL tyrosine kinase protein with the ligand molecule. However due to van der Waals forces and electrostatic attraction, Lyngbyabellin D1 showed highest binding score for which this drug was identified as the best drug for the treatment of BCR-ABL tyrosine kinase caused blood cancer.

The most effective management of the cancer is surgical removal of the cancerous tissue followed by radiation therapy. Curative treatment generally involves surgery, various forms of radiation therapy, or, less commonly, cryosurgery. Hormonal therapy is given with radiation in some cases. Hormonal therapy and chemotherapy are commonly reserved for cases of advanced disease [9]. Recently, [10] reported that Ponatinib was identified as drug (ligand) molecule among eleven important drugs such as Ponatinib, Bosulif, Synribo, Kyprolis, Urosolic acid, Boswellic acid, Hydroxy urea, 3-amino propanesulphonic acid, Imatinib, Dasatinib and Nilotinib against blood cancer causing receptor through *insilico* analysis. Currently various drugs like tamoxifen, raloxifene, apraclonidine, cocaine, dyclonine, lapatinib, hydroxy urea, ponatinib, imatinib, dasatinib, nilotinib and cabazitaxel have been prescribed for the control of various cancers. Cancer treatments do not have potent medicine as the currently available drugs are causing side effects in some instances [3]. The side effects of these drugs make the need for the necessity of new improved drugs and hence, in this investigation a new drug from cyanobacterial origin has been tried showing high binding affinity with the receptor molecule of blood cancer. In the present study Lyngbyabellin D1 is identified as the best drug molecule against blood cancer.

CONCLUSION

In this study, the molecular docking was applied to explore the binding mechanism and to correlate its docking score with the activity of compounds. The results of the present study can be useful for the design and development of novel compounds having better inhibitory activity against several type of cancer. This potential agent will be a promising candidate can further be validated in wet lab studies for its proper function. The Protein-Ligand interaction plays a significant role in structural based drug designing. BCR-ABL tyrosine kinase protein is the major enzyme responsible for the blood cancer. In order to identify the effectiveness of the cyanobacterial bioactive

compounds against blood cancer through molecular docking. Molecular docking between the receptor molecule (Bcr-Abl) and the ligand (cyanobacterial bioactive compound) molecules were carried out through which the binding efficiency and hydrogen bonding involved in the docking were determined. Among the various drugs used, Lyngbyabellin D1 with the receptor molecule Bcr-Abl showed high score binding and indicating that the Lyngbyabellin D1 is the effective and potential drug molecule for curing blood cancer.

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