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Synthesis, Single Crystal XRD and Molecular Docking of 3-α-Carboxy Ethyl Rhodanine

KAVERI SUNDARAM[1], SUBBAN RAVI[1,*], MUTHURAJAN THENMOZHI[2] and VEERAN MOHANRAJ[3]

[1]Department of Chemistry, Karpagam Academy of Higher Education, Coimbatore-641 021, India
[2]Centre for Nanotechnology and Advanced Biomaterials (CeNTAB), School of Chemical and Biotechnology, SASTRA University, Thanjavur-613 401, India
[3]Postgraduate & Research Department of Chemistry, Sri Ramakrishna Mission Vidyalaya College of Arts and Science, Coimbatore-641 020, India

*Corresponding author: E-mail: ravisubban@rediffmail.com

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The crystal product of 3-α-carboxy ethyl rhodanine was confirmed by single crystal XRD analysis. Furthermore, to examine the binding interactions of 3-α-carboxy ethyl rhodanine with the Bcr AblT315I tyrosine kinase and HPV 16 E2 protein molecular docking study was carried out. The results showed reasonable docking scores and displayed good interactions, thereby suggesting that 3-α-carboxy ethyl rhodanine may be used as a template for the further development of anticancer drugs.

Keywords: 3-α-Carboxy ethyl rhodanine, SXRD, Bcr AblT315I tyrosine kinase, HPV 16 E2 protein, Molecular docking.

INTRODUCTION

Owing to the excellent properties of rhodanine based molecules are one of the bioactive heterocyclic compounds and are used in various applications in industry, biochemistry and coordination chemistry. Rhodanine and their derivatives have broad industrial applications and widely used as intermediates in the syntheses of dyes, extreme-pressure lubricants and as brightening additives in silver electroplating. They also exhibit antioxidant properties as well as pharmacological [1] and biological activities including antibacterial [2], antiviral [3] and antidiabetical [4] properties. Due to their strong ability in donating electrons to metal ions, make them strong ligands in coordination compounds [5]. A rapid development in rhodanine chemistry was observed because of their use as inhibitors for protein mannosyl transferase-1 [6], phosphodiesterase-4 [7], protease [8], JSP-1 [9], UDP-N-acetylmuramate-L-alanine ligase [10], antimalerials [11], HIV-1 integrase [12-15] and β-lactamase [16]. Rhodanine nucleus containing commercial drug Epalrestat is used as aldose reductase inhibitor in some Asian countries [17,18]. In our earlier study reported that the *in vitro* cytotoxicity of a series of rhodanines found that 3-α-carboxy ethyl rhodanine was found to be more active against HeLa cell lines (IC_{50} = 10 μg/mL). The present work, we have reported the single crystal XRD of the active molecule 3-α-carboxy ethyl rhodanine for the first time. Further we have carried out *in silico* molecular docking studies against human cervical cancer oncoproteins HPV 16 E2 and a tyrosine kinase Bcr-Abl T315I protein to explore the possibility of using it as a lead molecule against cancers.

EXPERIMENTAL

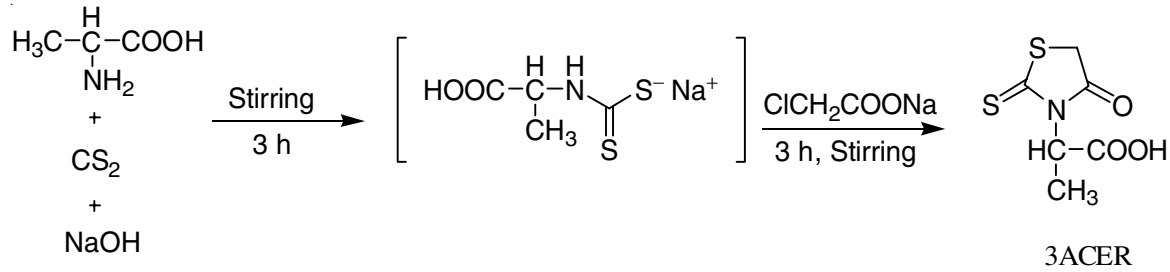
The commercially available chemicals used were of reagent grade and used without further purification. The single crystal X-ray diffraction data were obtained at 293 K on a Bruker SMART APEX2 CCD diffractometer.

Synthesis of 3-α-carboxy ethyl rhodanine (3ACER): 3-α-Carboxy ethyl rhodanine (3ACER) was prepared (**Scheme-I**) according to the method previously reported [19] and used for the single crystal XRD study.

Preparation of protein molecule and ligand: The trans-activation domain (TAD) receptor of human papillomavirus type 16 E2 protein (PDB ID: 1DTO) and the Bcr-Abl T315I (PDB ID: 2V7A) were retrieved from protein databank PDB [www.rcsb.org/pdb]. The obtained receptor was energy minimized by using Swiss PDB Viewer after adding hydrogen bond in AutoDock. 3ACER was constructed using ChemDraw Ultra 8.0 and 3-D structure was generated and optimized using AutoDock to acquire proper geometry.

RESULTS AND DISCUSSION

Crystal structure description of 3ACER: The asymmetric unit of 3ACER molecule structure comprises of 3-α-carboxy ethyl rhodanine molecule, an isolated sulphur atom and a water molecule, as shown in Fig. 1. The single X-crystal data of the



Scheme-I: Synthesis of 3-α-carboxy ethyl rhodanine (3ACER)

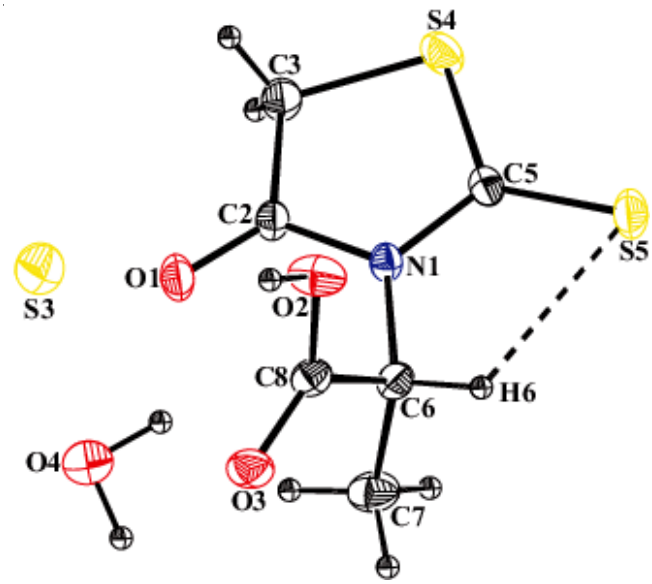


Fig. 1. ORTEP plot of **3ACER** molecule, showing 40 % probability displacement ellipsoids

synthesized compound is presented in Table-1. The atomic coordinate and equivalent isotropic displacement parameters for the non-hydrogen atoms of 3ACER are depicted in Table-2. In 3ACER, all the bond distances and bond angles are within the normal ranges (Tables 3 and 4). The five-membered ring in compound 3ACER is almost planar. The bond length of C3-S4 [1.794(3) Å] is almost in agreement with the carbon-sulphur single bond distance of 1.81. The internal angle C3-S4-C5 is 93.47(1)°, which is slightly larger than the expected angle of 90° for a single bond but the variation is in the correct direction for some double-bond character in the C3-S4 bond. The internal angle C2-N1-C5 is 116.06(2)° which again tends to show the resonance effect. The two parts of the molecule, the five-member heterocyclic group and the carboxylate group, which are oriented at a dihedral angle of 79.38(13)°. The double bonded, sulphur atom S5 at C5 and oxygen atom O1 at C2 are planar with the five-membered ring of 3-α-carboxy ethyl rhodanine molecule (maximum deviation for S5[-0.025(1) Å] and O1[0.058(2) Å]. The sum of the bond angles found to be around N1 is 359.99(6)°, which shows sp^2 hybridization.

The molecule connected through C-H···O, C-H···S and O-H···O hydrogen bonds (Fig. 2, Table-5). A short intramolecular contact distance of 2.615Å between S5 and H6, forming S(5) ring motif (Fig. 1); this distances significantly smaller than the sum (2.89 Å) of the van der Waals radii for S and H atoms [20,21]. There is another intramolecular O2-H2···O3 hydrogen bond between the oxygen atoms of carboxylate

TABLE-1
CRYSTAL DATA FOR 3ACER

Parameters	3ACER
CCDC	1035380
Empirical formula	$C_6H_9NO_4S_{2.50}$
Formula weight	239.29
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Monoclininc
Space group	P21/c
Unit cell dimensions	
a (Å)	12.6290(4)
b (Å)	8.2415(4)
c (Å)	9.9178(4)
β (°)	110.425(2)
Volume (Å^3)	967.36(7)
Z	4
Calculated density (Mg/m^3)	1.643
F(000)	496
Crystal size (mm)	0.10 × 0.10 × 0.20
θ range for data collection (°)	1.72 to 28.29
Limiting indices	-16 <= h <=15; -10 <= k <= 9 -13 <= l <= 13
Reflections collected/unique	7030/2375 [R(int) = 0.0234]
Completeness to θ = 25.00 (%)	99.70
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2375/3/132
Goodness-of-fit on F^2	1.111
Final R indices [I>2σ(I)]	R1 = 0.0451, wR2 = 0.1664
R indices (all data)	R1 = 0.0500, wR2 = 0.1755
Largest diff. peak and hole (eÅ^{-3})	0.529 and -1.344

TABLE-2
ATOMIC COORDINATES (× 10^4) AND EQUIVALENT ISOTROPIC DISPLACEMENT PARAMETERS (Å^2 × 10^3) FOR THE NON-HYDROGEN ATOMS OF 3ACER

Atoms	x	y	z	*U(eq)
C2	2618(2)	5292(3)	5829(2)	27(1)
C3	2028(2)	6761(3)	5021(3)	35(1)
C5	1198(2)	5559(3)	6821(2)	27(1)
C6	2561(2)	3236(3)	7613(2)	28(1)
C7	2348(2)	1715(3)	6702(3)	42(1)
C8	3800(2)	3508(3)	8534(2)	29(1)
N1	2112(2)	4695(2)	6752(2)	25(1)
O1	3448(2)	4666(2)	5710(2)	40(1)
O2	4008(2)	4901(2)	9149(2)	44(1)
O3	4492(2)	2422(2)	8690(2)	39(1)
O4	5978(2)	3147(3)	6993(2)	45(1)
S3	5000	5000	5000	55(1)
S4	906(1)	7212(1)	5680(1)	39(1)
S5	452(1)	5114(1)	7830(1)	43(1)

*$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i . a_j$

TABLE-3
SELECTED BOND LENGTHS (Å) OF 3ACER

Atoms	Length	Atoms	Length
C2-O1	1.210(3)	C5-S4	1.726(2)
C2-N1	1.378(3)	C6-N1	1.469(3)
C2-C3	1.499(3)	C6-C7	1.513(3)
C3-S4	1.794(3)	C6-C8	1.529(3)
C5-N1	1.379(3)	C8-O3	1.223(3)
C5-S5#1	1.637(2)	C8-O2	1.283(3)
C5-S5	1.637(2)	S5-S5#1	0.000(2)

Symmetry transformations used to generate equivalent atoms: #1 x,y,z

TABLE-4
SELECTED BOND ANGLES (°) OF 3ACER

Atoms	Angles	Atoms	Angles
O1-C2-N1	122.1(2)	N1-C6-C8	109.49(2)
O1-C2-C3	125.3(2)	C7-C6-C8	114.2(2)
N1-C2-C3	112.62(2)	O3-C8-O2	125.2(2)
C2-C3-S4	106.33(2)	O3-C8-C6	120.4(2)
N1-C5-S5#1	125.78(2)	O2-C8-C6	114.4(2)
N1-C5-S5	125.78(2)	C2-N1-C5	116.06(2)
S5#1-C5-S5	0.00(6)	C2-N1-C6	120.30(2)
N1-C5-S4	111.46(2)	C5-N1-C6	123.63(2)
S5#1-C5-S4	122.75(1)	C5-S4-C3	93.47(1)
S5-C5-S4	122.75(1)	S5#1-S5-C5	0.00(1)
N1-C6-C7	112.28(2)	–	–

Symmetry transformations used to generate equivalent atoms: #1 x,y,z

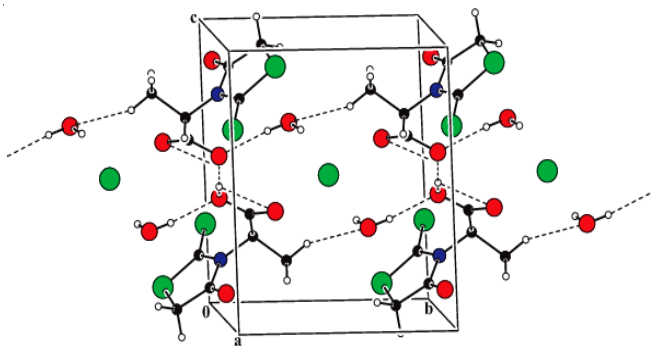


Fig. 2. View of the crystal packing of molecules, showing interactions along b-axis for 3ACER

TABLE-5
HYDROGEN BONDING GEOMETRY (Å AND °) FOR 3ACER

D–H···A	d(D–H)	d(H···A)	d(D···A)	∠(DHA)
C6–H6···S5[a]	0.98	2.61	3.152(2)	114.6
O2–H2···O2[b]	0.82	1.68	2.490(4)	169.4
O4–H4B···O2[c]	0.893(10)	2.026(13)	2.908(3)	169(4)
O2–H2···O3[b]	0.82	2.70	3.196(3)	120.6
C7–H7B···O4[c]	0.96	2.75	3.589(4)	145.9

Symmetry codes: (a)x,y,z (b) -x+1,-y+1,-z+2 (c) -x+1,y-1/2,-z+3/2

group, which generates an S(4) ring motif. 3-α-carboxy ethyl rhodanine molecules were connected *via* water molecules through C7-H7B···O4 and O4-H4B···O2 type of intermolecular interactions along b-axis. These molecules are further packed into stacks through O2-H2···O2 intermolecular interaction, view down a-axis.

Molecular docking: Docking of small-molecules into the binding site of a receptor and estimating the binding affinity of the complex is an important part of the structure based drug design process. In the recent past, lot of efforts were made to find new Bcr-Abl tyrosine kinase inhibitors which lead to the design and synthesis of new generation compounds.

Chronic myelogenous leukemia (CML) is caused by a chromosome mutation that leads to the formation of Philadelphia chromosome and is a consequence of fusion between the break point cluster (Bcr) gene at chromosome 22 and the Abelson (Abl) tyrosine kinase gene at chromosome 9 resulting in to an active Bcr-Abl tyrosine kinase that is responsible for chronic myelogenous leukemia.

Further, human papilloma virus (HPVs) are responsible for approximately half a million cases of cervical cancer every year and cause genital warts, which are one of the most common sexually transmitted diseases in many countries. This awareness has created new exciting approaches for preventing cervical cancer, which is the second most common malignancy of women worldwide [22]. The principal agent human papilloma virus (HPV) type 16, in the etiology of cervical cancer, encodes early proteins E1 and E2 and is involved with host cell systems to maintain and produce virus [23]. Loss of E2 function, which happens in early stage cancers, allows dysregulated expression of the viral on coproteins, E6 and E7 [24]. HPV E2 is binds with high affinity to specific sites in viral DNA and also binds to E1 and targets this replication factor to the viral origin of replication. So the molecular docking study was carried out for these two proteins.

To predict the binding mode of the 3-α-carboxy ethyl rhodanine, docking study was performed using AutoDockVina. The Lamarckian genetic algorithm (LGA) available in AutoDockVina was employed for docking. To perform molecular docking, the three-dimensional (3D) structure of 2VA7 (tyrosine kinase Bcr-Abl (T315I) protein) was obtained from Protein Data Bank and the ligand structure was drawn using Chem3D Ultra software. Further, 3D structure was prepared applying partial charges and energy minimization. The active site of the enzyme was defined in a manner so as to include residues of the active site within the grid size of 17.84, 9 22.59 and 9 20.77 Å. The docking protocol was tested by removing co-crystallized ligand from the protein and then docking it at the same site. The quality of the docking result was evaluated by computing the root-mean-square deviation (RMSD) between the docked pose and the known crystal structure conformation. RMSD values up to 2 Å are considered reliable for a docking protocol. The docking protocol we employed predicted a similar conformation with RMSD value well within the reliable range. The interactions were viewed using Chimera software packages.

The results for the binding energy and number of hydrogen bonds formed between the ligand and active sites are shown in Fig. 3. 3-α-Carboxy ethyl rhodanine showed binding energy between -4.1 and -4.8 kcal/mol due to the formation of hydrogen bonds with the active sites of Bcr-Abl (T315I), thereby suggesting effective inhibition. The carbonyl oxygen of the rhodanine moiety was engaged in a crucial hydrogen bond interaction with the N-H group of LYS271, which is in the ATP site and also with N-H of ASP381. The carboxy hydrogen forms hydrogen bon with the C=O group of ASN368 and ASP381, whereas the oxygen forms hydrogen bonds with the N-H group of ASN368.

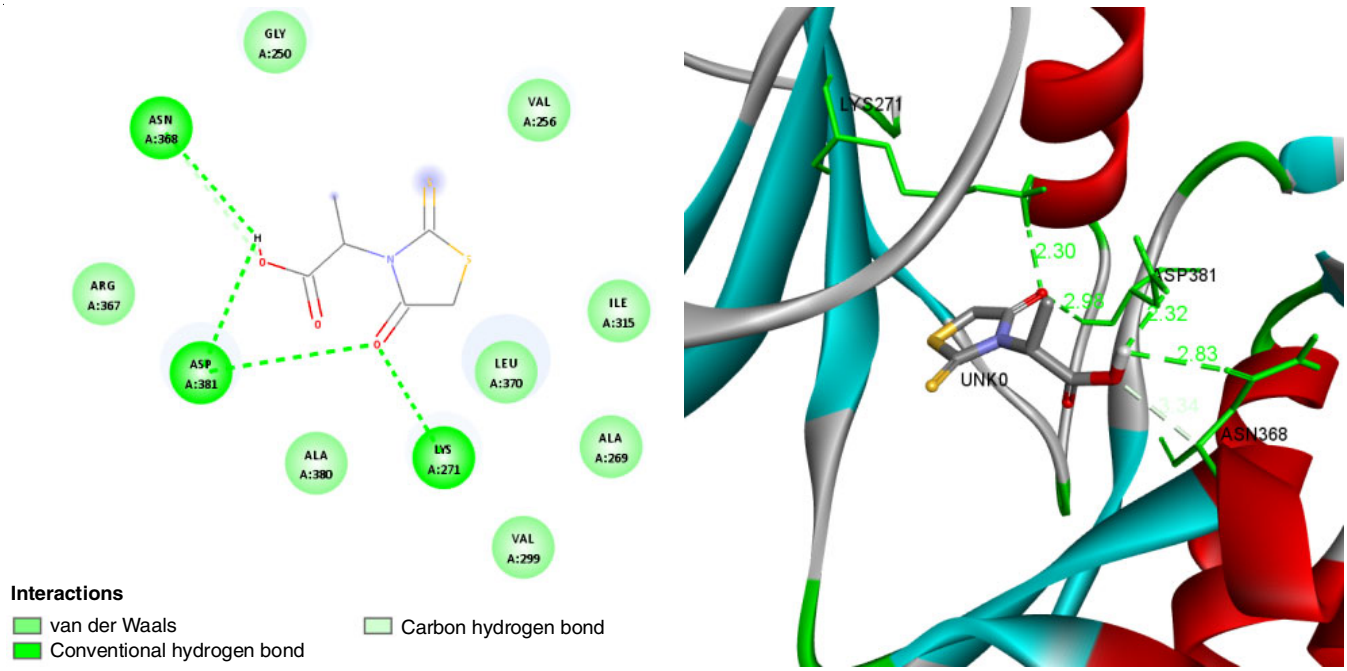


Fig. 3. Molecular docking of 3-α-carboxy ethyl rhodanine (3ACER) with Bcr-Abl T315I protein (PDB iD:2V7A)

Similarly the three-dimensional (3D) structure of 1 DTO (HPV E2 protein) was obtained from Protein Data Bank and docking was carried out with 3-α-carboxy ethyl rhodanine 3ACER. The carboxyl hydrogen forms hydrogen bonds with ARG37 and the rhodanine moiety showed effective hydrophobic interactions. It was learnt from the literature that the transcription and replication activities of E2 protein of human papillomavirus are controlled by a 200 amino acid N-terminal module (E2NT) and is connected to a DNA binding C-terminal module by a flexible linker [25]. The E2NT module from high-risk type 16 human papillomavirus has revealed an L-shaped molecule with two closely packed domains N1 and N2, each with a novel fold. The two principal functions of E2, transactivation and HPV DNA replication are controlled by the three conserved amino acids Arg37, Glu39 and Ile73 [26-29]. 3-α-Carboxy ethyl rhodanine 3ACER showed binding energy 4.5 kcal/mol (Fig. 4) and forms H-bonds with one of the conserved amino acids ARG37 which controls the two principal functions of E2, transactivation and HPV DNA replication. Since HPV is the major causative factor of cervical cancer, an inhibitor of HPV E2 may block progression to invasive cancer by inhibiting HPV replication. So, 3-α-carboxy ethyl rhodanine 3ACER binds well with the receptor HPV E2 protein (PDB id: 1DTO) and inhibits its function and thereby it can prevent the cervical cancer.

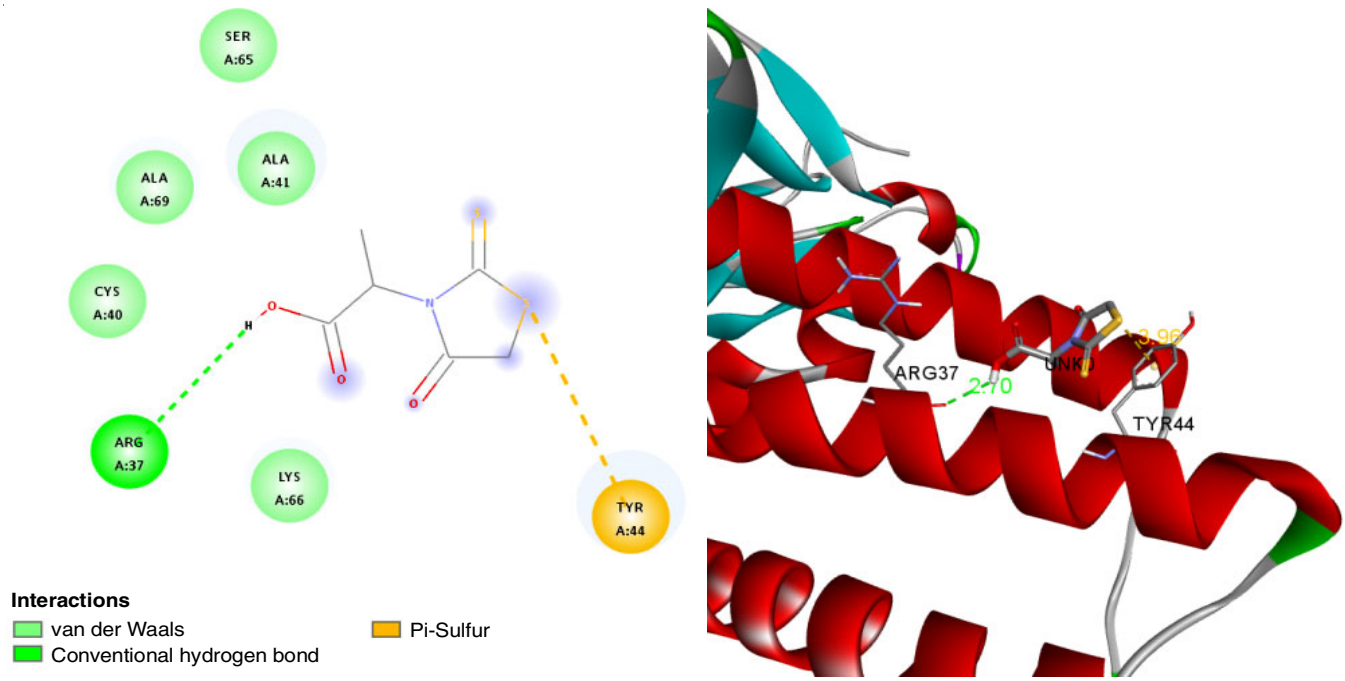


Fig. 4. Molecular docking of 3-α-carboxy ethyl rhodanine (3ACER) with HPV E2 protein (PDB iD:1 DTO)

Conclusion

The structure of the molecule 3ACER was confirmed by single crystal XRD analysis and it revealed a remarkable constancy of common bond lengths and angles. Molecular docking of 3ACER found to be potent inhibitor against HPV 16 E2 and Bcr-Abl T315I cancer proteins. It forms H-bonds with one of the conserved amino acids ARG37 of the HPV 16 E2 protein (PDB id: 1DTO) which controls the principal functions of E2, transactivation and HPV DNA replication, thereby a mechanism has been arrived. 3ACER may be used as a template for the further development of anticancer drugs.

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REFERENCES

1. B.C.C. Cantello, M.A. Cawthorne, D. Haigh, R.M. Hindley, S.A. Smith and P.L. Thurlby, *Bioorg. Med. Chem. Lett.*, **4**, 1181 (1994); https://doi.org/10.1016/S0960-894X(01)80325-5.
2. P. Villain-Guillot, M. Gualtieri, L. Bastide, F. Roquet, J. Martinez, M. Amblard, M. Pugniere and J.P. Leonetti, *J. Med. Chem.*, **50**, 4195 (2007); https://doi.org/10.1021/jm0703183.
3. S. Yan, G. Larson, J.Z. Wu, T. Appleby, Y. Ding, R. Hamatake, Z. Hong and N. Yao, *Bioorg. Med. Chem. Lett.*, **17**, 63 (2007); https://doi.org/10.1016/j.bmcl.2006.09.095.
4. R.F. Kletzien, S.D. Clarke and R.G. Ulrich, *Mol. Pharmacol.*, **41**, 393 (1992).
5. E.S. Raper, *Coord. Chem. Rev.*, **61**, 115 (1985); https://doi.org/10.1016/0010-8545(85)80004-7.
6. M.G. Orchard, J.C. Neuss, C.M.S. Galley, A. Carr, D.W. Porter, P. Smith, D.I.C. Scopes, D. Haydon, K. Vousden, C.R. Stubberfield, K. Young and M. Page, *Bioorg. Med. Chem. Lett.*, **14**, 3975 (2004); https://doi.org/10.1016/j.bmcl.2004.05.050.
7. M.W. Irvine, G.L. Patrick, J. Kewney, S.F. Hastings and S.J. MacKenzie, *Bioorg. Med. Chem. Lett.*, **18**, 2032 (2008); https://doi.org/10.1016/j.bmcl.2008.01.117.
8. S.L. Johnson, L.H. Chen, R. Harbach, M. Sabet, A. Savinov, N.J.H. Cotton, A. Strongin, D. Guiney and M. Pellecchia, *Chem. Biol. Drug Des.*, **71**, 131 (2008); https://doi.org/10.1111/j.1747-0285.2007.00617.x.
9. N.S. Cutshall, C. O'Day and M. Prezhdo, *Bioorg. Med. Chem. Lett.*, **15**, 3374 (2005); https://doi.org/10.1016/j.bmcl.2005.05.034.
10. M.M. Sim, S.B. Ng, A.D. Buss, S.C. Crasta, K.L. Goh and S.K. Lee, *Bioorg. Med. Chem. Lett.*, **12**, 697 (2002); https://doi.org/10.1016/S0960-894X(01)00832-0.
11. G. Kumar, P. Parasuraman, S.K. Sharma, T. Banerjee, K. Karmodiya, N. Surolia and A. Surolia, *J. Med. Chem.*, **50**, 2665 (2007); https://doi.org/10.1021/jm061257w.
12. R. Dayam, T. Sanchez, O. Clement, R. Shoemaker, S. Sei and N. Neamati, *J. Med. Chem.*, **48**, 111 (2005); https://doi.org/10.1021/jm0496077.
13. A.R. Katritzky, S.R. Tala, H. Lu, A.V. Vakulenko, J. Sivapackiam, Q.Y. Chen, K. Pandya, S. Jiang and A.K. Debnath, *J. Med. Chem.*, **52**, 7631 (2009); https://doi.org/10.1021/jm900450n.
14. G. Maga, F. Falchi, A. Garbelli, A. Belfiore, M. Witvrouw, F. Manetti and M. Botta, *J. Med. Chem.*, **51**, 6635 (2008); https://doi.org/10.1021/jm8008844.
15. S. Rajamaki, A. Innitzer, C. Falciani, C. Tintori, F. Christ, M. Witvrouw, Z. Debyser, S. Massa and M. Botta, *Bioorg. Med. Chem. Lett.*, **19**, 3615 (2009); https://doi.org/10.1016/j.bmcl.2009.04.132.
16. E.B. Grant, D. Guiadeen, E.Z. Baum, B.D. Foleno, D.A. Montenegro, H. Jin, E.A. Nelson, K. Bush and D. Hlasta, *Bioorg. Med. Chem. Lett.*, **10**, 2179 (2000); https://doi.org/10.1016/S0960-894X(00)00444-3.
17. P.F. Kador, J.H. Kinoshita and N.E. Sharpless, *J. Med. Chem.*, **28**, 841 (1985); https://doi.org/10.1021/jm00145a001.
18. R. Kikkawa, I. Hatanaka, H. Yasuda, N. Kobayashi, H. Terashima, Y. Shigeta, T. Morimura and M. Tsuboshima, *Diabetologia*, **24**, 290 (1983); https://doi.org/10.1007/BF00282716.
19. K. Sundaram and S. Ravi, *Asian J. Chem.*, **25**, 10353 (2013); https://doi.org/10.14233/ajchem.2013.15467.
20. A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964); https://doi.org/10.1021/j100785a001.
21. R.S. Rowland and R. Taylor, *J. Phys. Chem.*, **100**, 7384 (1996); https://doi.org/10.1021/jp953141+.
22. M.E. Sherman, S.S. Wang, J. Carreon and S.S. Devesa, *Cancer*, **103**, 1258 (2005); https://doi.org/10.1002/cncr.20877.
23. W.C. Phelps and P.M. Howley, *J. Virol.*, **61**, 1630 (1987).
24. B.A. Van Tine, L.D. Dao, S.Y. Wu, T.M. Sonbuchner, B.Y. Lin, N. Zou, C.M. Chiang, T.R. Broker and L.T. Chow, *Proc. Natl. Acad. Sci. USA*, **101**, 4030 (2004); https://doi.org/10.1073/pnas.0306848101.
25. A.A. Antson, J.E. Burns, O.V. Moroz, D.J. Scott, C.M. Sanders, I.B. Bronstein, G.G. Dodson, K.S. Wilson and N.J. Maitland, *Mol. Cell. Biol.*, **17**, 7208 (1997); https://doi.org/10.1128/MCB.17.12.7208.
26. D.E. Breiding, F. Sverdrup, M.J. Grossel, N. Moscufo, W. Boonchai, and E.J. Androphy, *Mol. Cell. Biol.*, 17, 7208 (1997); https://doi.org/10.1128/MCB.17.12.7208.
27. C.S. Cooper, S.N. Upmeyer and P.L. Winokur, *Virology*, **241**, 312 (1998); https://doi.org/10.1006/viro.1997.8941.
28. R.S. Hegde and E.J. Androphy, *J. Mol. Biol.*, **284**, 1479 (1998); https://doi.org/10.1006/jmbi.1998.2260.
29. J.M. Yao, D.E. Breiding and E.J. Androphy, *J. Virol.*, **72**, 1013 (1998).