

# Molecular Docking Studies of 3-A-Carboxy Ethyl Rhodanine and 3-A-Carboxy Methyl Rhodanine against T315i BCR-ABL and HPV 16

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## Abstract

In the present work, docking studies was performed for 32 selected rhodanine derivatives and it was evaluated their binding affinity to cancer proteins (PDB ID: 2V7A and 1D1O). Molecular docking was carried out using AutoDock 4.2.2 version and the visualization result using Chimera 1.10 and Discovery Studio 4.5. Among the 32 Compounds, T3151 Abl mutant protein (PDB ID: 2V7A) Showed a better Docking Score of compounds 1a, 1l and 2h. In HPV 16 protein (PDB ID: 1D1O) compounds 1e, 2f and 2g Showed better Docking Score. Overall, among all the 32 ligands the compound 2h Showed high docking score of -9 kcal/mol against protein.

**Keywords:** Molecular Docking, 3- $\alpha$ -Carboxy Ethyl Rhodanine and 3- $\alpha$ -Carboxy Methyl Rhodanine.

## INTRODUCTION:

Cancer is one of the harmful diseases in the world. In the past decades researchers and scientist have been face the task to find the effective medicine for the cancer. Apart from chemotherapy, radiotherapy and surgery it still remains the challenging one for the remedy of cancer [1]. Cancer cells are modified from their normal counterparts in a huge number of biochemical processes, particularly in terms of control the growth of cells and division. Despite the fact that major advances have been made for the prevention and treatment of cancer, chemotherapeutic agents generally play in metabolically active or normal cells as well, and cannot distinguish between cancer and normal cells [2]. Many chemotherapeutic agents are currently available in the market used for treatment of cancer, but the disease is still remains dangerous [3]. Thus, the search of new methods for novel anticancer agents with high efficacy, minimum side effects and low toxicity is a more active research area [4-5]. In the search for potential anticancer agents, maximum effort has been targeted on the development of chemotherapeutic agents that contain the heterocyclic group [6].

Rhodanine is a heterocyclic compound and it is used as a scaffold for the development of novel anticancer agents with wide range of cytotoxicity against many human cancer cells [7]. As previously reviewed [8], rhodanine and its derivatives are maximum evaluated for their anticancer activity against different cancer cell lines, often indicating the selective toxicity against cancer cell lines [9-12].

Here, molecular docking is used to determine the mechanism and to predict the binding orientation between the small molecules and the receptor and also to investigate the activity and affinity of the small molecules. The main aim of docking is to attain the conformation of protein and the ligands and to optimize the absolute orientation between the protein and ligands. The potential of the inhibitory compounds have been predicted by *insilico* methods. In this paper, we have made docking studies for the compound 3- $\alpha$ -carboxy ethyl rhodanine [13], 3-carboxy methyl rhodanine [14] and its derivatives against the proteins 2V7A and 1D1O.

## METHODS

### Molecular docking studies

Molecular docking study has been carried out using the PyRx. Version 0.8 docking program.

### Protein preparation

Target proteins (PDB ID: 1D1O and 2V7A) were downloaded from protein data bank.

### Ligand preparation

Two-dimensional structure of Ligands were drawn using ChemDraw Ultra. Discovery studio was used to convert 2D in to 3D structure and the energy was minimized using AM1 method. To minimise the energy to minimum RMS gradient of 0.100 was set in each iteration. All structures were saved as PDB file format. All the ligand structures were then saved in SDF file format, to carry out docking in Autodock vina.

### Grid formation

A grid box with dimension of 40 x 40 x 40Å with 0.37Å spacing and centered on 29.47, 47.99, 8.86 was created around the binding site on T3151 Abl mutant protein and HPV 16 using ADT. The centre of the box was set a ligand centre, and grid energy calculations were carried out.

## RESULT AND DISCUSSION

Molecular docking study against target proteins T3151 Abl mutant protein (PDB ID: 2V7A) and HPV 16 (PDB ID: 1D1O) involved in anticancer mechanisms was carried out for 32 compounds to see the binding affinity of the ligands and the receptor. To validate the docking method for the protein structures used, the corresponding ligands were docked to the active site of each protein using AutoDock4. The protein structures presented natural substrates as a co-crystallized ligand, whereas in others the co-crystallized ligand was a known inhibitor, in both cases the same docking and scoring validation process were used. Each co-crystallized ligand was previously removed from the respective protein binding site. The predicted docking pose was compared with the experimental co-crystallized binding pose.

The results are presented in Table 1. The docking score, hydrogen bonded residue, and hydrophobic interaction such as alkyl and pi alkyl, Vander Waals interaction were provided. Most of the ligands were showed very good interactions with the studied proteins. Among the 32 compounds studied, with the protein 1D1O,

The compound 1e, 2f and 2g showed a docking score of **-6.1, -6.7 and -6.7 Kcal/mol** with hydrophilic and hydrophobic interactions (fig 2). The compounds **1e, 2f and 2g** showed a better binding score with the HPV 16 protein (PDB ID: 1D1O). The compound **1e** with 1D1O protein forms a hydrogen bonding interaction with

THR A:81, TYR A: 102 and CYS A:140 and had pi-sigma interaction with LEU A:77. The compound 2f and 2g with IDTO protein forms hydrogen bonding interaction with GLN A:71, GLN A:95, TYR A:32 and pi-sigma interaction with LEU A: 99, SER A:98.

The compound 1a, 1l and 2h showed a docking score of **-7.2, -7.2 and -9 Kcal/mol** with hydrophilic and hydrophobic interactions (fig 3). The compounds **1a and 1l**, the ligand **2h** showed a good binding score with the T3151 Abl mutant protein (PDB ID: 2V7A). The compound 1a and 1l with 2V7A protein forms a

hydrogen bonding interaction with GLU A:286, LYS A:271, pi-sigma interaction with LEU A:248 and pi-alkyl interaction with ALA A:269, LEU A:370. The compound 2h with 2V7A protein forms a hydrogen bonding interaction with LYS A:271, ASP A:381, pi-sigma interaction with LEU A: 370 and pi-alkyl interaction with LEU A:248, ALA A:269, ALA A:380, VAL A:299 and ILE A:315. Comparing to the two proteins, the protein 2V7A showed a better score for all the ligands compare with IDTO protein.

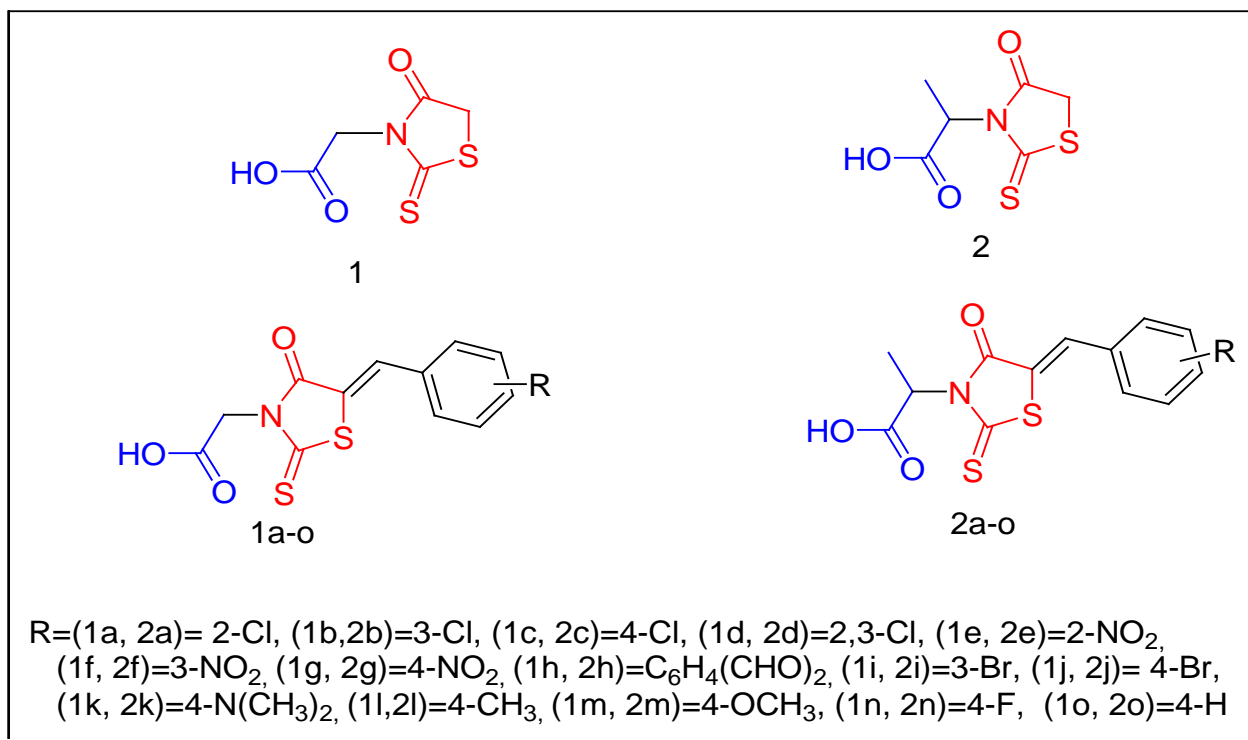


Fig 1: chemical structure of the ligands subjected for docking studies against anticancer target proteins

Table 1: docking score (kcal/mol) of the ligands with the two anticancer protein

ligands	IDTO	2V7A	ligands	IDTO	2V7A
1	-4.3	-4.7	2	-4.4	-4.6
1a	-5.5	<b>-7.2</b>	2a	-5.3	-7
1b	-5.3	-7	2b	-5.4	-7.2
1c	-5.5	-7	2c	-5.4	-7
1d	-5.5	-7.1	2d	-5.5	-7.2
1e	<b>-6.1</b>	-7.1	2e	-6.2	-8.2
1f	-5.5	-7.1	2f	<b>-6.7</b>	-8.3
1g	-5.3	-7	2g	<b>-6.7</b>	-8.7
1h	-5.6	-7.1	2h	-6.1	<b>-9</b>
1i	-5.4	-7	2i	-5.4	-6.9
1j	-5.4	-7	2j	-5.4	-7.2
1k	-5.6	-6.7	2k	-5.5	-7.2
1l	-5.2	<b>-7.2</b>	2l	-5.4	-7.3
1m	-5.4	-6.9	2m	-6.5	-8.8
1n	-5.5	-7	2n	-5.5	-7.2
1o	-5.2	-6.8	2o	-5.2	-6.9

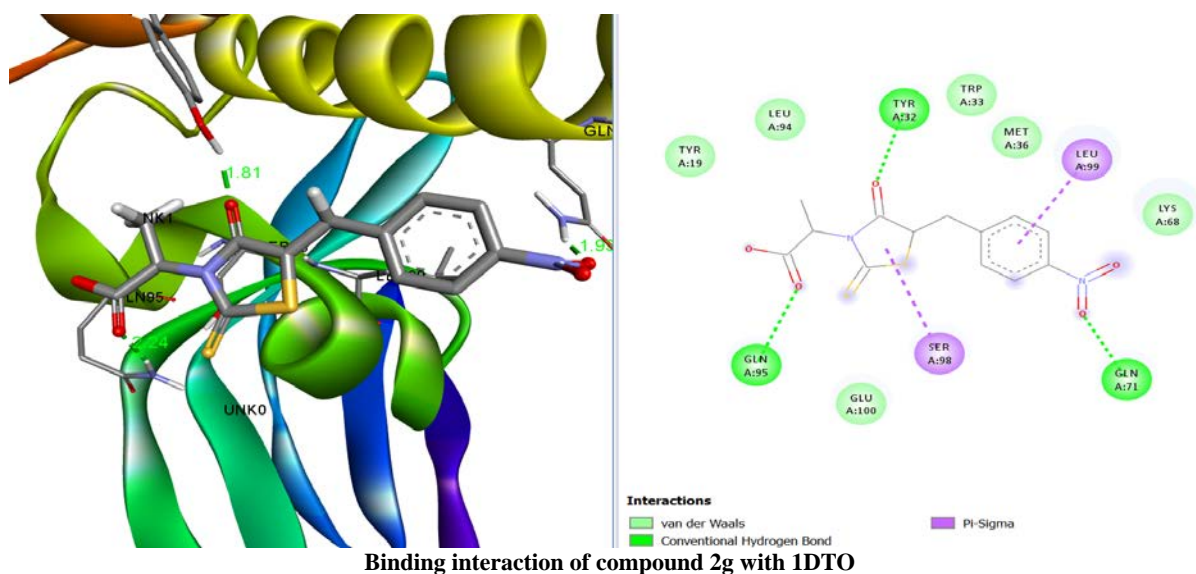
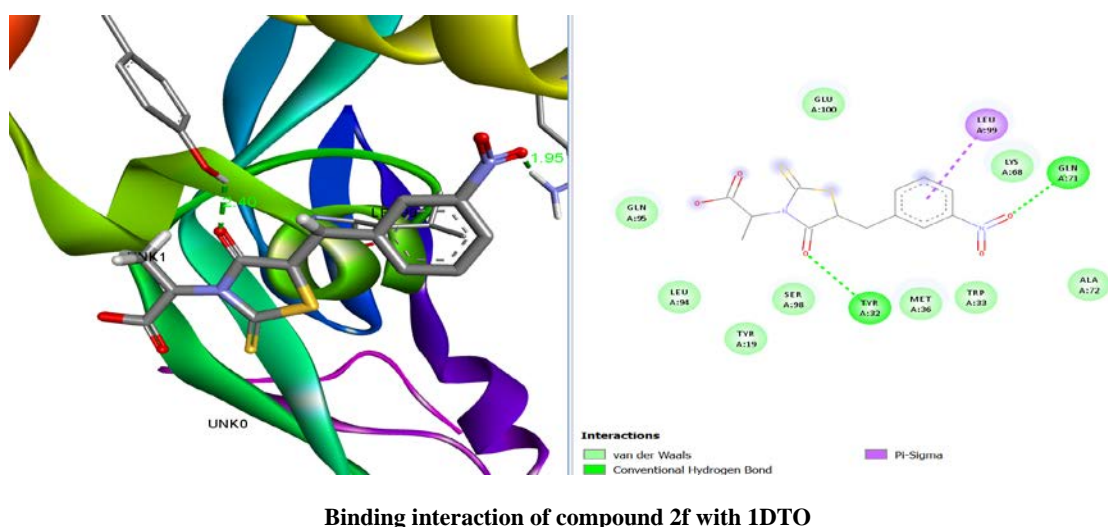
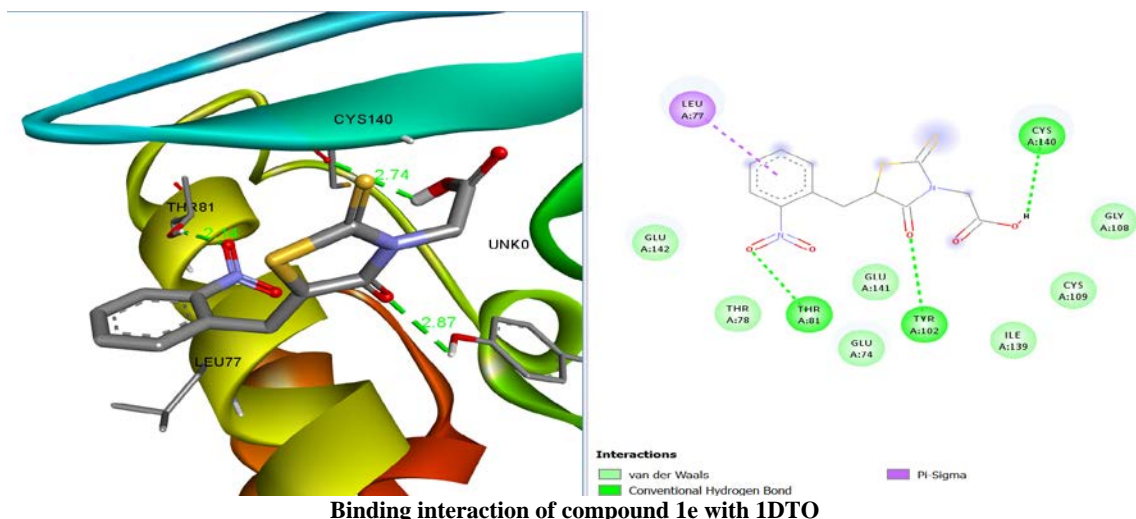


Fig 2: Three-dimensional(3D) and two-dimensional (2D) binding interaction of 1e, 2f and 2g with same protein( 1DTP)

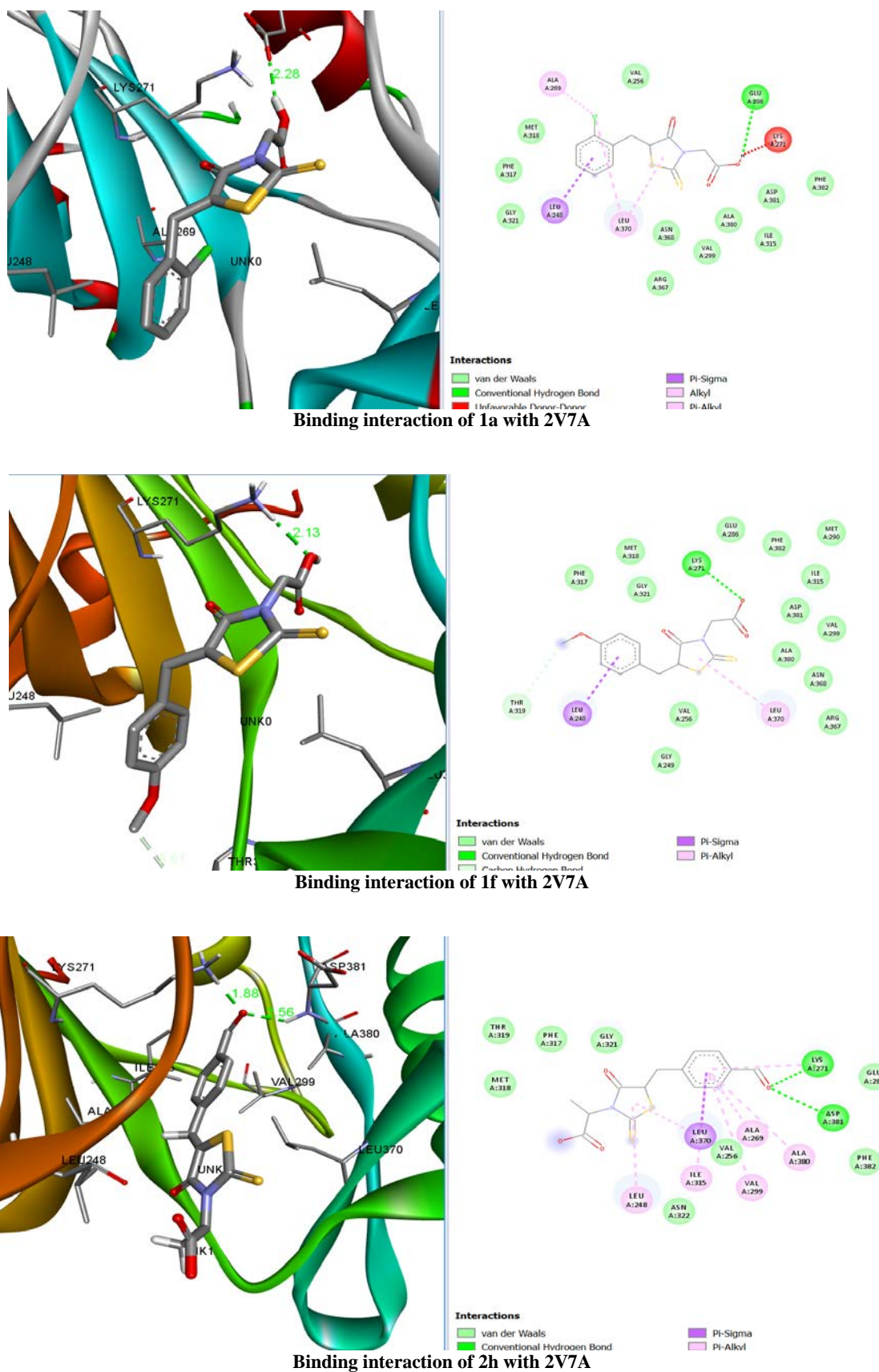


Fig 3: Three-dimensional(3D) and two-dimensional (2D) binding interaction of 1a,1f and 2h with same protein( 2V7A).

**CONCLUSION**

In docking computations, compound **2h** showed good binding mode and the existence of the electrostatic and hydrophobic interactions with the target protein. Overall, the results offer a valuable insight into the structural requirements for anticancer agents and thus provide a good foundation for further research in this field. Compound **2h** can serve as the lead compound for structural modification leading to design of novel anticancer studies.

**REFERENCES**

- De, M.; Jessica, K.; Boger, DL., *Drugs Future* **2008**, 33, 969–979.
- Kumar, CSA.; Swamy, SN.; Thimmegowda, NR.; Prasad, SB.; Yip, GW.; Rangappa, KS., *Med. Chem. Res.* **2007**, 16, 179–187.
- Curran, WJ., *Oncology.* **2002**, 63, 29–38.
- Sawyers, C., *Nature.* **2004**, 432, 294–297.
- Li, Q.; Xu, W., *Curr. Med. Chem. Anticancer Agents.* **2005**, 5, 53–63.
- Ip, M.M.; Sylvester, P.W.; Schenkel, L., *Cancer Res.* **1986**, 46, 1735–1740.
- Kumar, R.; Ravi, S.; Sundaram, K.; Venkatachalapathi, S.; Ali muhammad, S., *Indo American Journal of pharmaceutical Research.* **2015**, 5, 555-561.
- Ban, J.O.; Kwak, D.H.; Oh, J.H.; Park, E.J.; Cho, M.C.; Song, H.S.; Song, M.J.; Han, S.B.; Moon, D.C.; Kang, K.W.; Hong, J.T., *Chem. Biol. Interact.* **2010**, 188, 75–85.
- Havrylyuk, D.; Mosula, L.; Zimenkovsky, B.; Vasylenko, O.; Gzella, A.; Lesyk, R., *Eur. J. Med. Chem.* **2010**, 45, 5012–5021.
- Moorthy, B.T.; Ravi, S.; Srivastava, M.; Chiruvella, K.K.; Hemlal, H O.; Joy, S.C., *Raghavan, Bioorg. Med. Chem. Lett.* **2010**, 20, 6297–6301.
- Li, W.; Zhai, X.; Zhong, Z.; Li, G.; Pu, Y.; Gong, P. *Arch. Pharm.* **2011**, 344, 349–357.
- emal, A.; Bray, F.; Center, M.M.; Ferlay, J.; Ward, E.; Forman, D. *Cancer, CA, Clin, J.* **2011**, 61, 69–90.
- Sundaram, k.; Ravi, S., *Research on Chemical intermediates.* **2015**, 41, 1011-1021.
- Ali Muhammad, S.; Ravi, S.; Thangamani, A., *Med Chem Res.* **2016**, DOI 10.1007/s00044-016-1545-7