JOURNAL OF CRITICAL REVIEWS

ISSN- 2394-5125 VOL 7, ISSUE 04, 2020

Pharmacophores for Hsp-90 (heat shock protein 90) alpha for anti-cancer activity profile

P.G. Bansod

Department of Botany, VidyaBharatiMahavidyalaya, Amravati

Email: prafullabansod@rediffmail.com

Abstract: Despite multiple attempts, cancer is still a leading cause of millions of deaths around the globe. At present, chemotherapy is preferred over other options available for treatment of cancer. Nevertheless, a good number of ill-effects of anti-cancer drugs require to look for a better drug with high activity and low toxicity. For this, Hsp90 (heat shock protein 90), which is accountable for stability of several cancer related proteins in cancer cells of different types, is a promising target for developing an anti-cancer drug. The pharmacophore modeling could be beneficial to recognizedecisive pharmacophoric features to develop a Hsp90 inhibitor to cure cancer. In the present work, the same approach has been used, which led to development of a pharmacophoric pattern consisting of different features viz. lipophilic, H-bond donors and acceptors having a specific correlation and appearance.

Keywords: Hsp90 alpha, Cancer, Pharmacophore modeling

Introduction:

Cancer is responsible for millions of deaths;consequently, medicinal chemists are incessantlyworking to find out a drug that could suppress the development of cancer cells. In cancer cells, a protein Hsp90 (Heat Shock Protein 90, also known as HSPC) is expressed excessively[1]. It is anextremelypreserved, non-fibrous and chaperone protein with a crucial role in numerous cellular processes like appropriate folding of other proteins, programmed cell death, cell cycle regulation, cell viability,and degradation, and signalingprocesses [1-6]. As the name specifies, heat shock proteins (Hsp) safeguard cells when subjected to higher temperatures. The number “90” associated with Hsp90 indicates its weighs (90 kDa). There are two isoforms of Hsp90found in cytoplasm: Hsp90α (the inducible form) and Hsp90β (the constitutive form), which have 85% sequence identity with each other[1-6]. These two isoforms are like flexible biological catalysts and interact with a good number of newly synthesized proteinssuch as Akt2, CDKs, PKC, MAP kinases, steroid receptors, BCL-6, CAR, p53, Oct4, etc. to avoid their aggregation or mistakes in their folding [6]. However, in cancer cells, Hsp90α and Hsp90β are accountable for stability of a number of cancers producing proteinscompulsory for tumor growth, therefore causing to their overexpression [1-6]. Consequently, Hsp90 is an attractive target for developing a drug for cancer.

To achieve this goal, it is essential to know the prominent features associated with Hsp90 alpha inhibitors, which could be useful during drug discovery pipeline. In this regard, a simple and feasible approach is pharmacophore modeling. The approach provides the number and types of important structural features to be considered while developing a drug candidate. In the present

ISSN- 2394-5125 VOL 7, ISSUE 04, 2020

work, we have used consensus pharmacophore modeling. The results could be advantageous to develop a therapeutic candidate for Hsp90 alpha.

Materials and methods:

The present work is based on a dataset comprising imidazole moiety bearing inhibitors of hsp90 alpha. The datset was downloaded from BindingDB ((https://www.bindingdb.org/bind/index.jsp) and manually curated. The SMILES notations were converted to 3D-strcutures using OpenBabel [7], followed by MMFF94 optimization using Avogadro 2.0. Then, Open3DAlign software was used for their alignment. After that, the structures saved in 'mol2' file format. LIQUID [8,9], a free PyMOL plugin, was used to develop the consensus pharmacophore model using default settings. The data retrieved from BindingDB for highly active five molecules has been tabulated in Table 1 for the sake of convenience only.

S. N.	Binding DBReactant_set_id	Ligand SMILES	Binding DB Ligand Name	Target Name Assigned by Curator or DataSource	Target Source Organism According to Curator or DataSource	IC 50 (nM)	pIC 50-rounded
1	156543	CCOC(=O)NCc1ccc(cc1)-n1c(n[nH]c1=S)-c1cc(C(C)C)c(O)cc1O	BX-2819	Heat shock protein HSP 90-alpha	Homo sapiens	0.04	10.3 98
2	156540	CCOC(=O)NCc1ccc(cc1)-n1c(n[nH]c1=S)-c1ccc(O)cc1O	Ethyl carbamate analog, 3	Heat shock protein HSP 90-alpha	Homo sapiens	0.1	10
3	156542	CC(C)c1cc(-c2n[nH]c(=S)n2-c2cccc3ccccc23)c(O)cc1O	lspropyl analog, 5	Heat shock protein HSP 90-alpha	Homo sapiens	0.1	10
4	156541	CCc1cc(-c2n[nH]c(=S)n2-c2cccc3ccccc23)c(O)cc1O	Ethyl analog, 4	Heat shock protein HSP 90-alpha	Homo sapiens	0.2	9.69 9
5	156538	Oc1ccc(-c2n[nH]c(=S)n2-c2cccc3ccccc23)c(O)c1	DC23:: Resorcinol analog, 1	Heat shock protein HSP 90-alpha	Homo sapiens	0.3	9.52 3

It is to be noted that curated dataset consists of more than 1800 molecules. The complete dataset is available on request from author.

ISSN- 2394-5125 VOL 7, ISSUE 04, 2020

Results and Discussion:

The consensus pharmacophore modeling led to identification of important features, which have been depicted in Figure 1. From Figure 1, it is clear that lipophilic (green contour), H-bond acceptor (Red contour) and H-bond donor (Blue contour) are prominent features.

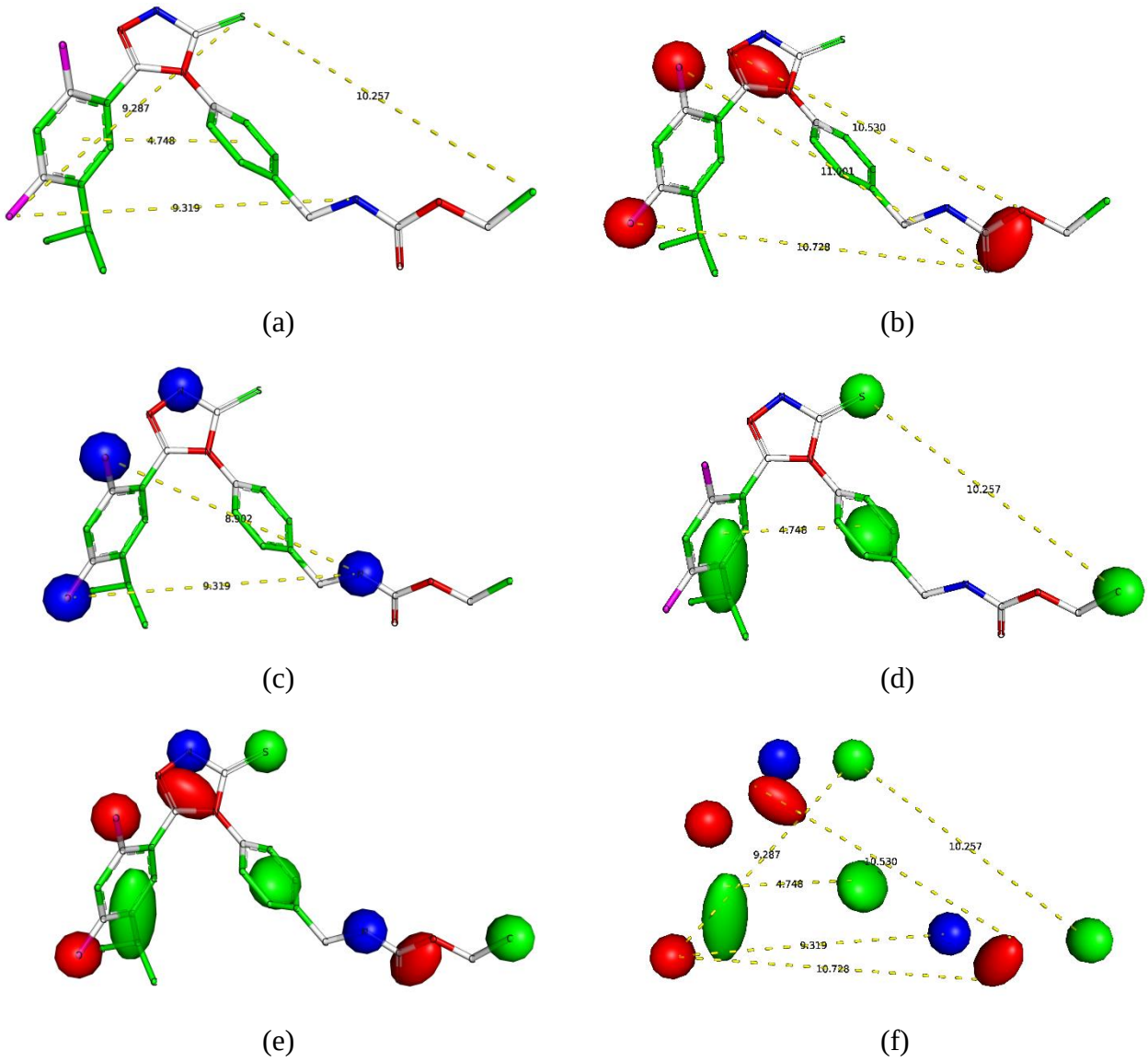

Figure 1. Depiction of lipophilic (green contour), H-bond acceptor (Red contour) and H-bond donor (Blue contour) regions of Hsp90 alpha inhibitors. Distances in Angstrom unit have been shown using yellow dashed line.

A closer analysis reveals that there are four H-bond donor, two acceptor and four lipophilic regions in the Hsp90 alpha inhibitors. The central portion of inhibitors consists of lipophilic

ISSN- 2394-5125 VOL 7, ISSUE 04, 2020

region, whereas majority of H-bond acceptors and donors are located near the periphery or outer regions. The position and number of H-bond capable moieties and lipophilic regions indicates that the inhibitor has a good balance of required moieties, which could be a reason for its high activity viz. 0.04 nM (see table 1). Therefore, in future optimizations, a balance of these regions is required for high activity profile.

Conclusions:

In conclusion, the present work is successful in identifying the significant structural features associated with anti-cancer activity of Hsp90 alpha. The inhibitor must consist of an equilibrium of lipophilic and H-bond capable regions. The lipophilic regions must be situated at the center of the molecule, while the H-bond forming groups at the outer part. The results could be beneficial to researcher during drug discovery optimization of different trial candidates.

Acknowledgment: Sincere thanks to Principal, VidyaBharatiMahavidyalaya, Amravati for providing necessary facilities and support.

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