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Pharmacophore mapping of diverse classes of farnesyltransferase inhibitors

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Abstract—Protein farnesyltransferase (FTase) is a zinc-dependent enzyme that catalyzes the attachment of a farnesyl lipid group to the sulfur atom of a cysteine residue of numerous proteins involved in cell signaling including the oncogenic H-Ras protein. Pharmacophore models were developed by using Catalyst HypoGen program with a training set of 22 farnesyltransferase inhibitors (FTIs), which were carefully selected with great diversity in both molecular structure and bioactivity for discovering new potent FTIs. The best pharmacophore hypothesis (Hypo 1), consisting of four features, namely, one hydrogen-bond acceptor (HBA), one hydrophobic point (HY), and two ring aromatics (RA), has a correlation coefficient of 0.961, a root mean square deviation (RMSD) of 0.885, and a cost difference of 62.436, suggesting that a highly predictive pharmacophore model was successfully obtained. For the test series, a classification scheme was used to distinguish highly active from moderately active and inactive compounds on the basis of activity ranges. Hypo 1 was validated with 181 test set compounds, which has a correlation coefficient of 0.713 between estimated activity and experimentally measured activity. The model was further validated by screening a database spiked with 25 known inhibitors. The model picked up all 25 known inhibitors giving an enrichment factor of 10.892. The results demonstrate that the hypothesis derived in this study can be considered to be a useful and reliable tool in identifying structurally diverse compounds with desired biological activity.

Inhibition of farnesyltransferase (FTase) has generated much attention recently as a promising target for the treatment of a broad spectrum of cancers due to their reduced intrinsic toxicity as compared to the conventional cytotoxic agents.[1] FTase catalyzes the transfer of a farnesyl moiety from farnesyl pyrophosphate to a cysteine residue found in the tetrapeptide sequence CAAX (C = Cys, A = an aliphatic amino acid, X is typically Met)[2] in the carboxyl terminal of a group of membrane-bound small G-proteins such as Ras, RhoB, RhoE, lamin A and B, and transducin. FTIs can stop protein farnesylation and suppress the growth of Ras-dependent tumor cells. Hence, over the last two decades, several researchers synthesized different classes of FTIs, such as SCH66336 (Sarasar™) and R115777 (tipifarnib or Zanestra™), which are currently in advanced stages of human clinical trials.[3–5] Our literature survey revealed that FTIs in different classes possess 19 different scaffolds (Fig. 1). Thus, quantitative structure–activity relationship (QSAR) analysis of different classes of inhibitors could be utilized for extracting out valuable information for developing new potent FTIs. The pharmacophore mapping is a well-established approach to quantitatively explore common chemical features among a considerable number of structures with great diversity, and qualified pharmacophore model could also be used as a query for searching chemical databases to find new chemical entities.

In the present study, we have generated pharmacophore model using Catalyst[6–8] software for diverse set of molecules of FTIs with an aim to obtain pharmacophore model that could provide a rational hypothetical picture of the primary chemical features responsible for activity. This is expected to provide useful knowledge for developing new potentially active candidates targeting the FTase, which can be useful as cytotoxic agents.

Selection of molecule. Pharmacophore modeling correlates activities with the spatial arrangement of various

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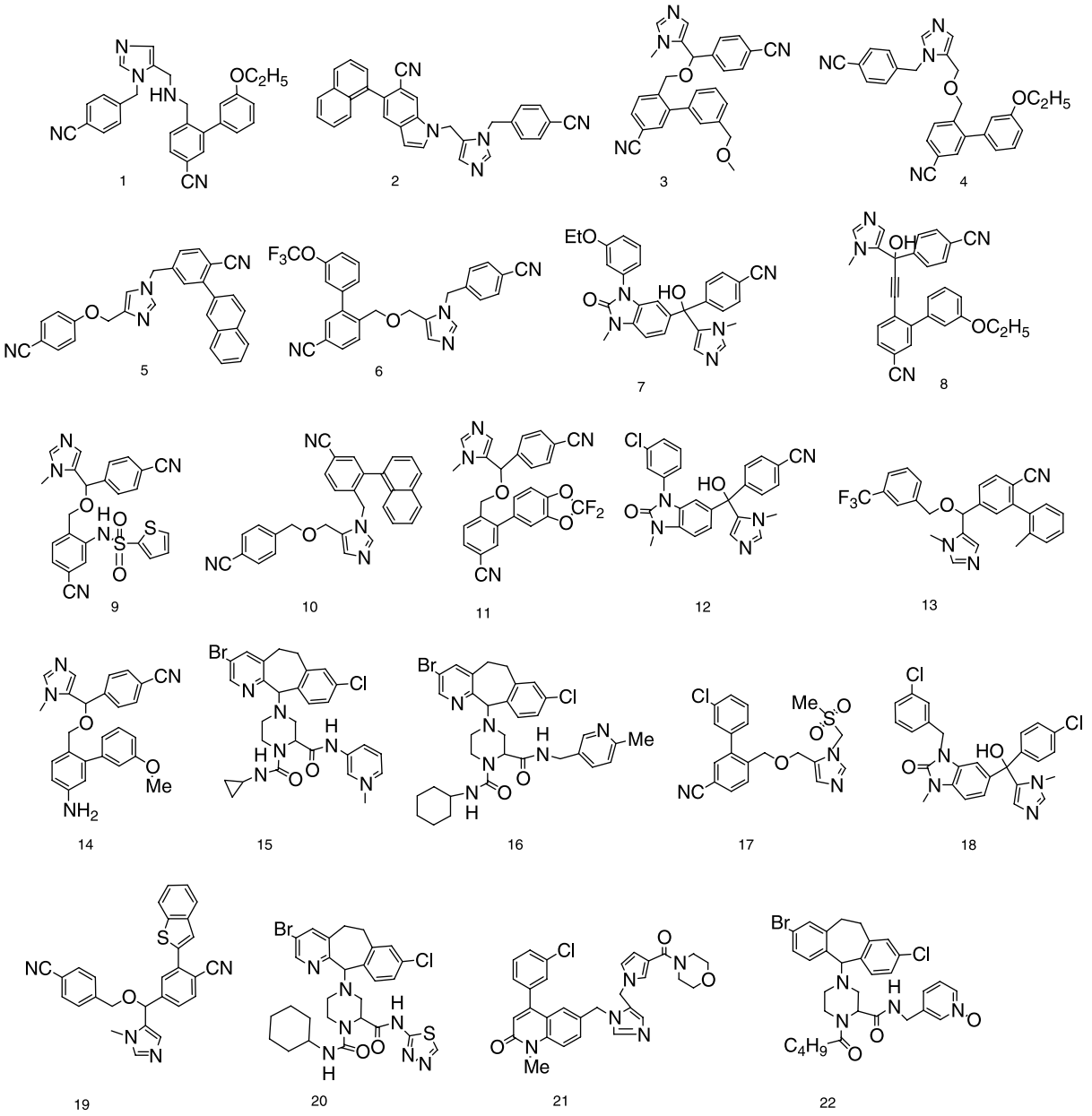

Figure 1. Chemical structures of the 22 training set molecules applied to HypoGen pharmacophore generation.

chemical features. For the pharmacophore modeling studies, a set of 203 farnesyltransferase inhibitory activity data (IC_{50}) spanning over 5 orders of magnitude (from 0.014 to 1800 nM) were selected from the literature.[9–16] The dataset was divided into training set and test set. The training set was selected by considering both structural diversity and wide coverage of the activity range. The most active, several moderately active, and some inactive compounds were also included in order to obtain critical information on pharmacophore requirements. The important aspect of this selection scheme was that each active compound would teach something new to the HypoGen module to help it uncover as much critical information as possible for predicting biological activity. The training set consisted of 22 compounds selected with the above criteria (Fig. 1 and Table 1). To validate our pharmacophore, the other 181 compounds were used as the test set (Table L in Supporting information). The activities (IC_{50}) against FTase are reported to be classified as: highly active (<10 nM), moderately active (10–100 nM), and inactive (>100 nM). All the IC_{50} values were obtained using the same assay method.[17]

Molecular modeling. The structures of all the compounds were built from fragments in Catalyst 4.10. A CHARMM like force field[18] in the Catalyst program was utilized to ascertain the energy-minimized conformations for each structure. Details of the pharmacophore development procedures have been described in the literature.[19,20] Initially, conformational models of all molecules for FTase datasets were generated using the 'best quality' conformational search option within the Catalyst ConFirm module using the 'Poling'