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RESEARCH PAPER

Pharmacophore modeling and 3D QSAR studies for prediction of matrix metalloproteinases inhibitory activity of hydroxamate derivatives

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Abstract In order to develop potent inhibitors of matrix metalloproteinase (MMP-2 and MMP-9) as anticancer agents, pharmacophore modeling and three-dimensional quantitative structure–activity relationship (3D-QSAR) models were established using PHASE 3.0. A pharmacophore 5-point (AAARR) model was developed for the studied dataset and the generated model was used to derive the predictive atom-based 3D-QSAR models. After identifying a valid hypothesis, we developed 3D-QSAR models applying the PLS algorithm. The selected 3D-QSAR models were suggestive of the vitality of the electron-withdrawing feature for the MMPs inhibitory potential. In addition, hydrophobic groups, hydrogen bond donor groups, positive ionic and negative ionic features also positively contributed to the MMPs inhibitory potential along with the electron-withdrawing feature. The developed models were statistically robust (MMP-2 $Q^2 = 0.51$; pred $R^2 = 0.67$; MMP-9 $Q^2 = 0.59$; pred $R^2 = 0.77$). The QSAR results help in identifying a relationship between structural features of hydroxamate derivatives and their activities which could be useful to design newer MMP inhibitors.

Introduction

Cancer cells possess a broad spectrum of migration and invasion mechanisms and metastasis is one of the major causes for mortality in cancer patients. Highly malignant cancers have metastasis as an important characteristic with poor clinical outcome. Malignant tumor progression mainly depends upon the capacity to invade, metastasize, and to promote the angiogenic host response. Metastasis cancer cells have acquired one critical characteristic; that is the ability to dissolve the extracellular matrix (ECM) and basement membranes (Rathee, Thanki, Bhuva, Anandjiwala, & Agrawal, 2013). The growth of a tumor and its ability to metastasize mainly depends on angiogenesis (Folkman, 1971). In addition, angiogenesis is critically important for embryo and female reproductive cycles vascular remodeling and also for wound healing specifically in the adults.

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However, aberrant angiogenesis occurs in certain pathological conditions, like diabetic retinopathy, psoriasis, cancer, hemangiomas, and rheumatoid arthritis (Liekens, Clercq, & Neyts, 2001). Since, endothelial cells invasion/migration into surrounding tissues/stroma involves in angiogenesis, proteases like matrix metalloproteinases (MMPs) are vitally significant.

MMPs belongs to a family of zinc-dependent, calcium-containing endoproteinases which are involved in degradation of ECM components and tissue remodeling at the physiological pH values, mainly in cell motility and angiogenesis (Kontogiorgis, Papaioannou, & Hadjipavlou-Litina, 2005). MMPs are involved in various processes such as ovulation, implantation of the blastocyst, development of embryo, morphogenesis, nerve growth, tissue remodeling and resorption (in wound healing case), bone remodeling, arthritis (both osteoarthritis and rheumatoid arthritis), gastric ulceration, corneal and skin ulcer, multiple sclerosis, angiogenesis, apoptosis, cancer invasion and metastasis, pulmonary emphysema, rupture of atherosclerotic plaque, aortic aneurysms, congestive heart failure, breakdown of blood-brain barrier, Crohn's disease, periodontal disease, psoriasis, dermatitis and Alzheimer's disease (Scozzafava & Supuran, 2000). Virtually, all human cancers generally abundantly express MMPs. MMPs expression from tumor stromal cells passing through paracrine secretion of growth factors and cytokines is induced by cancer cells (Egeblad & Werb, 2002). High levels of expression of certain MMPs, either by the infiltrating inflammatory cells, by the tumor cells themselves or by stromal fibroblasts, are correlated with poor prognosis and metastatic potential and/or tumor invasion (Vihinen & Kähäri, 2002). Several mechanisms are involved for the role of MMPs in the cancer progression. At first, it was taken into consideration that the MMPs mediate metastasis and invasion chiefly by matrix remodeling thus allowing tumor cells access to lymphatic and blood vessels. The fact for this mechanism is mainly based on the increased cell lines invasiveness, which further over expresses the MMPs. In recent times, it is evident that MMPs can play a role in primary tumor growth and it involves the release of MMP-mediated tumor angiogenesis or stroma-bound growth factors (Summers & Davidsen, 1998).

Recently, it turn out to be crystal clear about the more complex role of MMPs in angiogenesis rather than simply degrading the ECM in order to facilitate the invading endothelial cells (Liekens et al., 2001; Stetler-Stevenson, 1999). Also, it is evident about the multiplicity and complexity of the signals that commence and sustain angiogenesis. Growth factors and proangiogenic cytokines include fibroblast growth factors (FGFs), angiopoietins, vascular endothelial growth factors (VEGFs), transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), platelet-derived growth factors (PDGFs), interleukin-8 (IL-8), epidermal growth factor (EGF), and angiogenin which are secreted by pericytes, keratinocytes (during epidermal wound healing), inflammatory cells (such as macrophages and mast cells), or tumor cells. Some of these growth factors and proangiogenic cytokines act by binding directly to their respective receptors present on endothelial cells to induce migration and/or proliferation, whereas in order to stimulate angiogenesis others act on inflammatory cells or local stromal cells (Li, Zhang, & Kirsner, 2003; Weinstat-Saslow & Steeg, 1994). For the ''angiogenic switch'' in cancer angiogenesis, MMP-2 and MMP-9 (gelatinases) have been shown to be significant when cancers (or preneoplastic lesions) become vascularized for the first time. In angiogenic islets, MMP-2 and MMP-9 expression was up-regulated in comparison with preangiogenic islets, however, it was determined that MMP-2 expression contributed to cancer growth (using MMP knockout mice), while MMP-9 expression was important for angiogenic switch (Yu & Stamenkovic, 2000). Invasion and metastasis capability, and/or risk of recurrence have been correlated in particular with tumor expression of MT1-MMP and various other MMPs (such as MMP-1, -2, -3, - 7, -9, -13) (Vihinen & Kähäri, 2002).

The MMPs inhibition has been the subject of intense research interest in the pharmaceutical industry in recent years (Johnson, Dyer, & Hupe, 1998; Morphy, Millican, & Porter, 1995; Zask, Levin, Killar, & Skotnicki, 1996). Various available synthetic MMP inhibitors are classified as tetracycline analogues, hydroxamates, carboxylates, barbiturates, thiols, phosphonates, etc. (Subramaniam, Malik, & Srivastava, 2009). The design of new MMPs inhibitors provides an opportunity to develop new drug candidates, as in several pathological states aberrant MMPs activities are involved (Mori et al., 2013). The design of various MMPs inhibitors for use as therapeutic agents has been an exceptionally active area of research, specifically in the treatment of arthritis and cancer (Skiles, Gonnella, & Jeng, 2001; Zask et al., 1996).

For the speedy discovery and development of novel anticancer therapeutic agents, the technological advancement and broader application of experimental methods grasp vast assurance as foundations. To achieve this target, computer-aided drug discovery (CADD) has become progressively more important, due to certain advantages such as much less investment in technology, time is required and resources (Wilson & Muftuoglu, 2012). Various cases of structure-based drug design's successful applications have been reported in the recent years (Combs, 2007; Coumar et al., 2009; Khan et al., 2010; van Montfort & Workman, 2009). With the help of computational methods, the chemical compounds with potentially higher affinity for the target can be rationally designed by utilizing the given three dimensional structure of a target molecule. Based on this pharmacophore model (binding site-derived), the results consist of a compilation of virtual ligands complementary to a three dimensional structure of the binding pocket- a pattern of putative interaction sites (Wilson & Muftuoglu, 2012). During the identification of p53 upregulated modulator of apoptosis (PUMA) inhibitors structure-based pharmacophore modeling was successfully used (Mustata et al., 2011).

Several QSAR studies have been published for hydroxamate derivatives (Gupta, 2015; Stephen, Nicolas, Cécile, & Martin, 2001). Previously reported studies discussed various QSAR (Nirmala, Adimulam, & Seetharamaiah, 2016, chap. 4; Roy, Pal, De, & Sengupta, 2001; Zheng, Wen, & Guillaume, 2008) approaches against MMPs (MMP-1, MMP-2, MMP-8, MMP-9, MMP-13), however, 3D-QSAR (three-dimensional quantitative structure–activity relationship) approach was not discussed. Nermala et al. employed multiple regression procedure to perform QSAR analysis on a set of 72 α-sulfone hydroxamate MMP-13 inhibitors. Roy et al. performed QSAR analyses on N-[(substituted