Short Communication

Computational drug design in the search of protein tyrosine phosphatase 1B_inhibitors as potential antidiabetic agents

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INTRODUCTION: Computational approaches, including both indirect and direct designs have been used in the search of novel small molecules as potential biologically active agents. The protein tyrosine phosphatase 1B (PTP1B) is been considered is potential targets for designing for antidiabetic agents as PTP1B inhibition results both in increased insulin sensitivity and resistance to obesity, with no abnormalities in growth or fertility or other pathogen etic effects.

CASE PRESENTATION: Thus in search of small molecule as potential PTP1B inhibitors, the indirect drug design approaches like CoMFA, CoMSIA and pharmacophore modeling resulted in the design and synthesis of a series of 2-[(4-methoxyphenyl) ethyl] acetamide derivatives including a promising PTP1B inhibitor (IC50 = 69µM) and another series of substituted phenoxy-3-piperazin-1-yl-propan-2-ols where one compound showed 40.3% normalization of plasma glucose levels at 100mg/kg in sugar-loaded model (SLM) and 32% activity in streptococci model (STZ).

CONCLUSION: Careful patient selection is needed to ensure a favorable risk-benefit ratio. Also a thorough multidisciplinary evaluation of patient and the possible therapeutic options is necessary, in order to create an optimal and individualized treatment plan hydatid nature of the lesion. The definitive diagnosis remains histological and the treatment is always surgical. We report an observation of a breast hydatid cyst discovered incidentally.

Keywords: *Endocrine; Drug design; Molecules*

Key Words: *Neurological Disorder; Endocrinology; Hydrogen bond*

INTRODUCTION

Computational approaches, including both indirect and direct designs have been used in the search of novel small molecules as potential biologically active agents. The protein tyrosine phosphatase 1B (PTP1B) is been considered is potential targets for designing for antidiabetic agents as PTP1B inhibition results both in increased insulin sensitivity and resistance to obesity, with no abnormalities in growth or fertility or other pathogenetic effects. Thus in search of small molecule as potential PTP1B inhibitors, the indirect drug design approaches like CoMFA, CoMSIA and pharmacophore modeling resulted in the design and synthesis of a series of 2-[(4-methoxyphenyl) ethyl] acetamide derivatives including a promising PTP1B inhibitor (IC50 = 69µM) and another series of substituted phenoxy-3-piperazin-1-yl-propan-2-ols where one compound showed 40.3% normalization of plasma glucose levels at 100mg/kg in sugar-loaded model (SLM) and 32% activity in streptozocin model (STZ). In continuation of this work using computer assisted pharmacophore modeling and direct drug design approaches like docking led to the identification and synthesis of substituted sulfonamides and carboxamides where the best compound of the sulfonamides and carboxamides series showed very high activity with IC50 values 7.54 and 5.8µm respectively. Both the compounds improved in vivo activity in STZ model and restored the insulin level and the serum lipid profile by significantly improving the insulin signaling and insulin resistance. Altogether, both compounds present excellent profile for development.

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Protein tyrosine phosphatase 1B (PTP1B) is an attractive target for treating cancer, obesity, and type 2 diabetes. In our work, the way of combined ligand- and structure-based approach was applied to analyze the characteristics of PTP1B enzyme and its interaction with competitive inhibitors. Firstly, the pharmacophore model of PTP1B inhibitors was built based on the common feature of sixteen compounds. It was found that the pharmacophore model consisted of five chemical features: one aromatic ring (R) region, two hydrophobic (H) groups, and two hydrogen bond acceptors (A). To further elucidate the binding modes of these inhibitors with PTP1B active sites, four docking programs (AutoDock 4.0, AutoDock Vina 1.0, standard precision (SP) Glide 9.7, and extra precision (XP) Glide 9.7) were used. The characteristics of the active sites were then described by the conformations of the docking results. In conclusion, a combination of various pharmacophore features and the integration information of structure activity relationship (SAR) can be used to design novel potent PTP1B inhibitors.

Diabetes mellitus has grown up to be a serious health problem around the world. According to the World Health Organization (WHO), 422 million people around the world suffered from diabetes in 2016, up from 108 million people in 1980, and its prevalence is projected to be 764 million by 2030. The majority of these people suffered from type 2 diabetes (T2D), whose cause is insufficient insulin secretion in peripheral tissues. Type 2 diabetes is extraordinarily associated with a variety of severe complications such as cardiovascular, eye, kidney, and nervous system diseases and diabetic nephropathy. There are numerous oral diabetes medicines approved by the FDA, such as Invokana, Lyxumia, Nesina, and even Glucophage. Although great efforts have been made in this field, the therapeutic efficacy of market products is greatly limited by serious side effects and complicated drug-drug interactions in combination therapy. To solve these intractable problems, the main direction is to still search for new therapeutic agents. Protein tyrosine phosphatase 1B (PTP1B), a negative regulator of insulin and leptin signaling pathways, is a promising target for the development of type 2 diabetes treatment.