PRELIMINARY INVESTIGATION OF COMMON GSK3, PPARγ AND DPP IV CHEMICAL SPACE

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Abstract

Cross-target biochemical experiments demonstrated that some molecules display an ample spectrum of biological activities which are therapeutically effective. In this regard we investigated the chemical space of the following targets GSK3, DPP IV and PPAR gamma since the DPP IV inhibitors, and PPAR gamma agonists are used to treat diabetes miellitus of type 2. Nevertheless, GSK-3 inhibitors have shown therapeutic potential for insulin resistant type-2 diabetes, the drug market does not register yet an inhibitor of GSK-2 for therapeutical use. The ChEMBL homo sapiens assay data for GSK-3, DPP IV and PPAR gamma were assembled into are database including 7599 compounds. GSK-3 assay comprise 2497 compounds, from which 1889 are unique divided into 428 chemotypes. DPP IV register 3482 compounds and 3026 were unique sharing 510 chemotypes. PPAR gamma incldes 1620 agonists from which 1333 are unique partitioned into 264 chemotypes. The chemical space of GSK3, DPP IV and PPAR gamma share 12 chemotypes, GSK3 and DPP IV share 30 chemotypes, DPP IV and PPAR gamma share 13 chemotypes, whereas GSK3 and PPAR gamma share 17 chemotypes. The 12 chemotypes active on all three proteins were superposed to develop a common pharmacophore which will be further used to identify novel chemotyes with potential biological activity.

Introduction

In this study we investigated the chemical space of the following targets: Glycogen Synthase Kinase-3 (GSK-3)[1] and Dipeptidyl Peptidase IV (DPP IV) inhibitors [2] and Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) [3] agonists which are used to treat diabetes miellitus of type 2.

Sitagliptin (original brand name Januvia) is a highly selective DPP IV inhibitor, used in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a PPARγ agonist (e.g., thiazolidinediones)[2].

Our goal was to detect shape similar compounds with Sitagliptin (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihidro[1,2,4]triazolo[4,3-A]pirazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine (PDB code: 4FFW_715) conformer cocrystallized with DPP IV. To accomplish our goal aRapid Overlay of Chemical Structures(ROCS) search was performed using the above mentioned sitagliptin conformation.Further we investigate the commom pharmacophore point to identify a possible common interaction pattern.

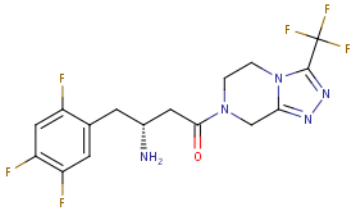

Figure 1.The structure of sitagliptin DPP IV inhibitor used as query

Methodology

The dataset used in our study was downloaded from the ChEMBL [4] database, to obtain bioactive compounds on GSK-3, DPP IV and PPAR gamma, whch asseembled resulted in 7599 compounds.
In the fisrt step the active compounds were filtered for duplicates using InstantJChem [5] software resulting 6248 unique compounds from which 1889 active compounds were for GSK-3, 3026 active compounds for DPP IV, and 1333 active compounds for PPAR gamma.
In the second step these unique compounds were divided into 428 chemotypes for GSK-3, 510 chemotypes for DPP IV and 264 chemotypes for PPAR gamma using Bemis Murko frameworks from InstantJChem [5] software.
In the third step were found 12 common chemotypes for the all proteins from where we extracted 12 active compounds with the highestIC_{50}.
Thesitagliptin conformation was downloaded from the RCSB Protein Data Bank [6] and the bond orders were checked.
The input for ROCS [7] analysis were the conformers of the 12 compoundswhose affinities were measured against all hereby investigated proteins which were generated with Omega version 2.3.2 from OpenEye [8] package using by default settings (RMSD = 0.8 Å, a energy window of 10 kcal, maximum output conformers 400.

Results and Discussions

The shape similarity search with ROCS has been proved to produce fast and reliable results that guarante good quality alignment.
All the conformes were overlaid, over the X-ray structure (4FFW_715) [4]) and thirteen similarity functions TanimotoCombo, ShapeTanimoto, ColorTanimoto, FitTverskyCombo, FitTversky, FitColorTversky, RefTverskyCombo, RefTversky, RefColorTversky, ScaledColor, ComboScore, ColorScore, Overlap implemented in ROCS were calculated [7-10].
The minimal, maximal and mean values of the most important similarity coefficients resulted from the similarity searches against the query (Figure 1) are listed in Table 1.

Table 1. The minimal, maximal and mean values of Tanimoto coefficients

Query (4FFW_715)	TC*	ST*	SC*	CS*
min	0.479	0.338	0.13	0.6
max	1.531	0.848	0.71	1.558
average	0.72051	0.485677	0.316521	0.818698

*TC-TanimotoCombo, ST-ShapeTanimoto, SC-ScaledColor, CS-ComboScore

The distributions of the minimal, maximal and mean values of important tanimoto similarity functions are shown in Figure 2

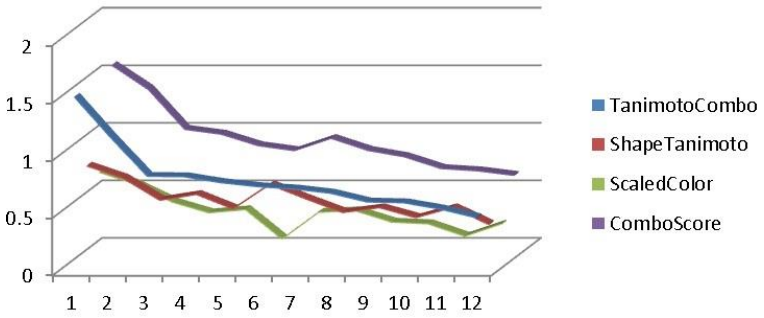

Figure 2. The distribution of the Tanimoto Combo, Shape Tanimoto, Scaled Color and Combo Score

The first 10 molecules ranked by ROCS were DPP IV inhibitors bearing different substituents (Figure 3). As expected, it can be observed (Figure 3) that these compounds align very well to the sitagliptin conformation.

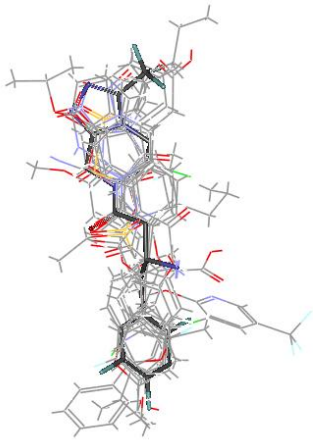

Figure 3. Alignment of the top 10 hits (line) to the RX ligand (stick) [11].

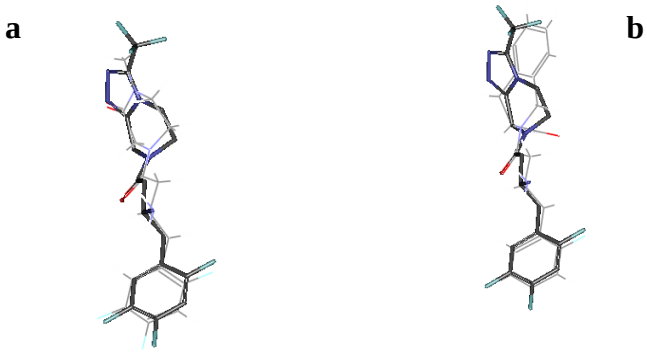

Figure 4. Superposition of the X-ray structure of the ligand (stik) and the corresponding best overlayed conformation for CHEMBL1779688 (line) (a) and CHEMBL381806 (line)(b)[11].

The best superposition compounds whose corresponding shape TanimotoCombo is of 1.531 CHEMBL1779688 (Figure 4a) and ComboScore (including Shape + ColorScore) values (1.347)

corresponds CHEMBL381806 (Figure 4b) [11].These values are good enough to suggests structural similarity, but also a certain degree of scaffold hopping.

Conclusions

The 7599 compounds downoladed from ChEMBL database with experimentally determined IC_{50} were involved in our final study.The ROCS analysis provided 12 active compounds for all tree protein with common chemical space.The 12 compounds active on all three proteins were superposed to develop a common pharmacophore which will be further used to identify novel chemotyes with potential biological activity.

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