PHARMACOPHORE BASED SCREENING AND QSAR ANALYSIS OF STRUCTURALLY DIVERSE COMPOUNDS FOR LEAD SELECTION AND OPTIMIZATION AGAINST MULTIPLE TARGETS

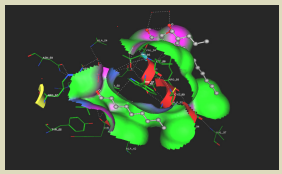
N.S. Hari Narayana Moorthy, Maria J. Ramos and Pedro A. Fernandes

REQUIMTE - Departamento de Química & Bioquímica, Faculdade de Ciências do Porto, 687, Rua do Campo Alegre, Porto, 4169-007, Portugal (hari.moorthy@fc.up.pt)

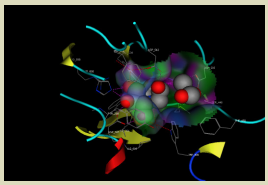
In the present investigation, structurally diverse molecules possessed α-glucosidase, RNR, FTase and hERG inhibitory activities were considered for this analysis. The bioactive conformers derived from the pharmacophore based conformer analysis (PBCA) method were used for the QSAR analysis. The results were used to interpretate the active site features of the enzyme/protein and was compared witht the analog enzyme/proteins from the Protein Data Bank.

Figure 3 : Active site environment of the enzymes/proteins

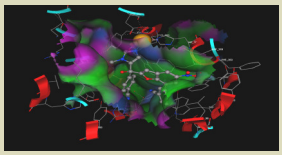
hERG protein (PDB ID: 1R3J)



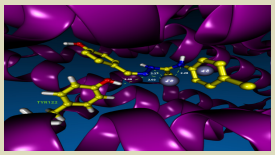
α-Glucosidase (PDB ID: 2QMJ)



Ftase (PDB ID: 2ZIS)

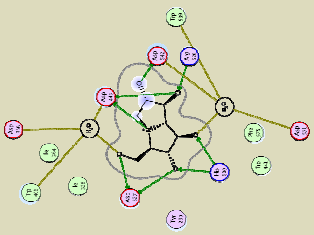


RNR (PDB ID: 1MXR)

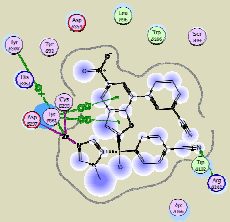


LIGAND INTERACTIONS

α-Glucosidase (PDB ID: 3CTT)



Ftase (PDB ID: 2ZIS)



DISCUSSION:

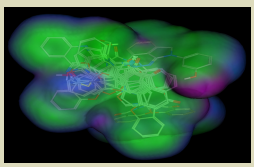
The QSAR results derived from different targets (α-glucosidases, RNR, FTase and hERG) provided significant results (Fig. 2). The statistical parameters calculated for the models show that the developed models are statistically significant and have predicted the activities with small residual errors. The Q^2 values obtained from different validation methods (LOO, LMO, LSO and test set) show >0.7 and the significant R^2_{pred} and R^2_m values reveal that the selected models are reliable and robust.

The bioactive pharmacophoric conformers were also used for the docking analysis on the targets. The results obtained from the studies suggest that the vdW surface property of the molecules is important for the activity. The flexible bonds and the presence of aromatic rings have better activity against the targets. It is supported by the active site environment of the enzymes/proteins.

The results obtained from the QSAR and the pharmacophore analyses agree with the active characters (environment) of the enzyme/protein obtained from the literature (Fig. 3).

On the basis of the QSAR results pharmacophore contours and the active site characters of the proteins, novel lead structure was optimized in order to design novel moieties. The hERG and toxicity data of the novel lead compounds designed is provided in Table 1. The flexialigned structure of the lead compounds provided in Fig. 4.

Figure 4: Flexialigned structure of the lead compounds



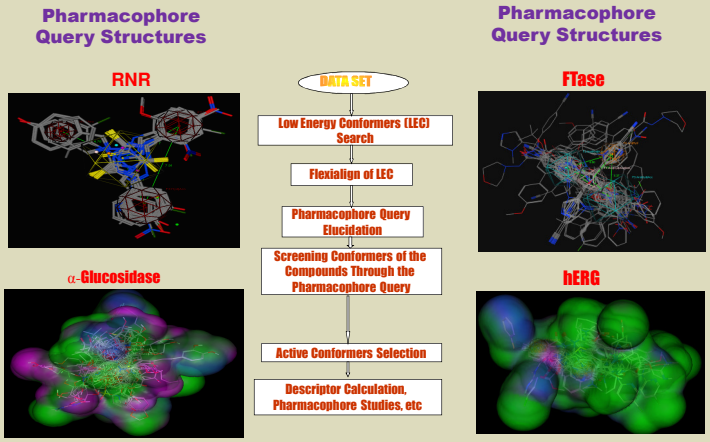
CONCLUSION:

Results of these studies and the ongoing research in our laboratory (other molecular modeling studies) were used to develop novel molecules. It can be a better drug designing with the consideration of the pharmacodynamic and pharmacokinetic compatibility of the molecules/lead to improve the success rate of the molecules.

ACKNOWLEDGEMENT

One of the authors N.S.H.N. Moorthy is grateful to the Fundacao para a Ciencia e Technologia (FCT), Portugal for a Postdoctoral Grant (SFRH/BPD/44469/2008).

FIGURE 1: FLOW CHART FOR PHARMACOPHORE BASED CONFORMERS ANALYSIS (PBCA) METHOD AND RESULTS



Experimental: The flexialigned structure of the active compounds in the series and the reference compounds were considered as the query pharmacophore structures. The flowchart of the Figure 1 has been followed for the active conformers generation. The developed QSAR models were validated by various validation methods (LMO, LOO, LSO, bootstrapping, Y-randomization and test set).

Figure 2: QSAR Results Obtained for the Studies

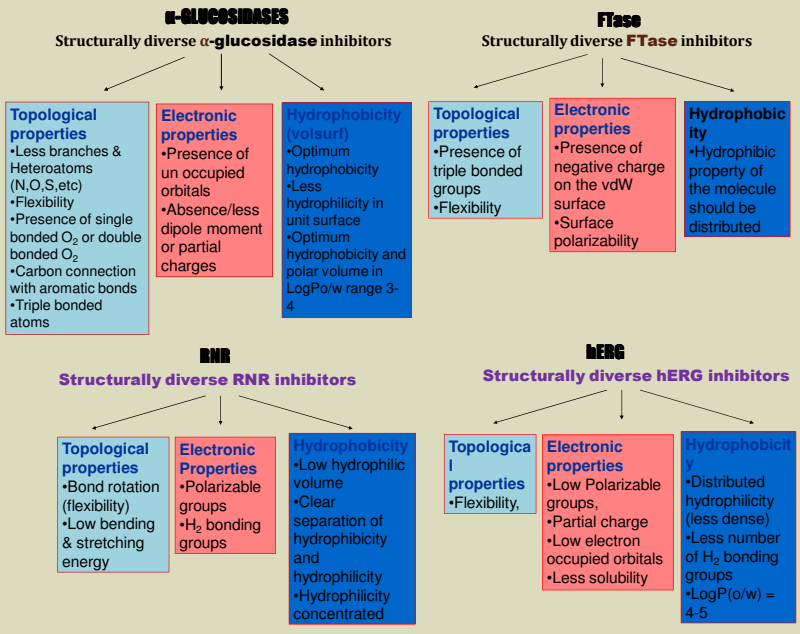


Table 1: PREDICTED hERG, TOXICITY AND OTHER STRUCTURAL PROPERTIES

Name	HERG	-LD_{50}	logP	Solubi.	MW	DMSO	Lipinsk
LEAD-1	2.2	0.5	3.4	0.036	250.3	69.6	True
LEAD-2	2	0.4	3.3	0.035	251.2	146.1	True
LEAD-3	2.1	0.6	3.2	0.034	252.2	306.6	True
LEAD-4	1.8	0.4	2.6	0.008	251.2	77.2	True
LEAD-5	2.3	0.7	4	0	275.3	29.3	True
LEAD-6	2.1	0.9	3.4	0.001	259.3	27.7	True
LEAD-7	2.2	0.9	3.3	0.001	260.2	58.1	True
LEAD-8	0.9	1.2	0.3	2.69	216.2	221.3	True
LEAD-9	**4.1**	**1**	**3.5**	**0.023**	**307.3**	**157.5**	**True**
LEAD-10	2.5	0.4	3.2	0.034	252.2	306.6	True
LEAD-11	**6.2**	**0.5**	**3.8**	**0**	**341.4**	**9.2**	**True**
LEAD-12	**5.2**	**1.2**	**4**	**0**	**328.4**	**65.2**	**True**
LEAD-13	3.8	1	2.9	0.024	278.3	99.4	True

References:

- N.S.H.N. Moorthy, M.J. Ramos, P.A. Fernandes, J. Enz. Inhibit. Med. Chem. 2011, 26(1), 78-87; Lett. Drug Des. Dis. 2011, 8, 14-25; J. Enz. Inhibit. Med. Chem. 2011 DOI: 10.3109/14756366.2010.549089; J. Biomol. Screen., DOI: 10.1177/1087057111414899.
- N.S.H.N. Moorthy, N.S. Cerqueira, M.J. Ramos, P.A. Fernandes, Med. Chem. Res., (Article in Press). DOI: 10.1007/s00044-011-9580-x.
- Choe, H., Nah, K.H., Lee, S.N., Lee, H.S., Lee, H.S., Jo, S.H., Leem, C.H., Jang, Y.J., Biochem. Biophy. Res. Comm., 2006, 344, 72-78
- MOE, Chemical Computing Group, Montreal, Canada, 2008
- q-ADME, q-hERG and q-Tox softwares, Quantum Pharmaceuticals. Moscow, Russia.