MINING THE EPI-RELEVANT CHEMICAL SPACE:

SEARCHING FOR NOVEL BROMODOMAIN INHIBITORS, USING FLEXIBLE ALIGNMENT AND DOCKING

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BACKGROUND

Recently the field of epigenetics has grown significantly. However as of today few studies have focused on the context of this information. The epigenetically relevant chemical space (ERCS) with special attention to BRDi, HDACi and DNMTi has been previously presented[1].
In the light of found similarities with approved drugs and GRAS compounds a virtual screening was conducted for BRDi using fungal metabolites[2], alkaloids, and others.

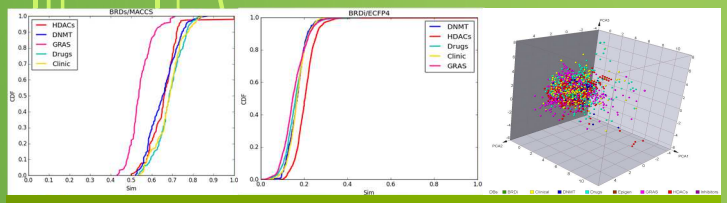


Figure 1. Chemography of ERCS, a) Interlibrary similarities calculated with MACCS keys in MOE; b) Interlibrary similarities calculated from Extended Connectivity fingerprints (ECFP4); c) Chemical space representation by PCA from SlogP, TPSA and molecular weight.

Methods

- Querie searches were conducted for the data sets listed in Table 1
- For 2D similarity comparison, MACCS keys and Extended Connectivity Fingerprints (ECFP4) were used.
- Additional hits were obtained by 3D flex-allignment to diverse ligands of BRDs obtained from PDB[4].
- Potential hits were docked to BRD4 structure for cross validation of selected compounds.

Data set	Size (number of compounds)	Number of unique molecules	Source	URL/ Reference
FDA Drugs	>5000	1490	Drugbank	www.drugbank.ca/drugs/
Fungi	224	207	Fungal Metabolites	González-Medina et al., 2016. Fut. Med. Chem. *In press*
NP	365	245	Pubchem	www.pubchem.ncbi.nlm.nih.gov/
Benzimidazoles	91	91	In-house	Aguayo-Ortiz et al. 2014. Fut. Med. Chem.
GRAS	2200	2200	FEMA	Medina-Franco et al. 2012. PLOS One

Table 1. Summary of datasets used on the current study

RESULTS

PDB ID	Chemotype	BRD
4J1P	Methoxyquinazolone	2
5BT5	Benzimidazole	
3S92	Benzotriazepine	3
3P5O	Benzodiazepine	4
4CFL	Piperazinechromenone	
4YH4	Pyrroledione	

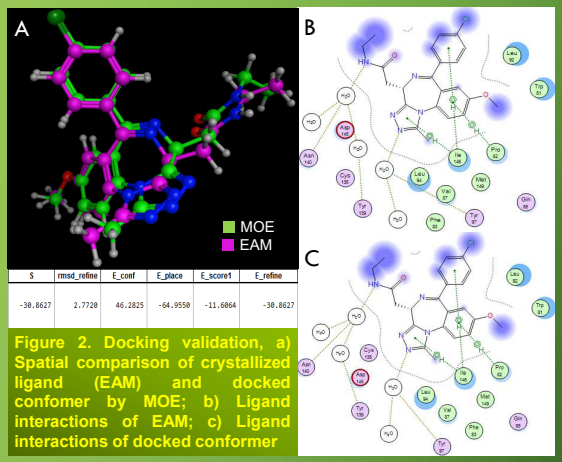
Table 2. PDBs used as queries for virtual screening protocol

Database	Hits recovered
FDA	70
Fungi-NP	20
GRAS	44
Benzimidazole	5

Table 3. Hits recovered per data set by flexible alignment method

Almost 5000 compounds were analyzed, yielding 520 hits considering 2D and 3D similarity.

To begin the virtual screening the docking protocol was validated using PDB ID: 3P5O[3]



S	rmsd_refine	E_conf	E_place	E_score1	E_refine
-30.8627	2.7720	46.2825	-64.9550	-11.6064	-30.8627

Figure 2. Docking validation, a) Spatial comparison of crystallized ligand (EAM) and docked confomer by MOE; b) Ligand interactions of EAM; c) Ligand interactions of docked conformer

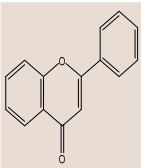
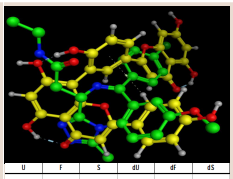
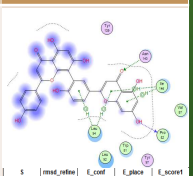
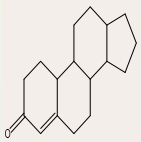
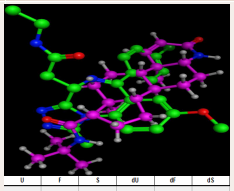
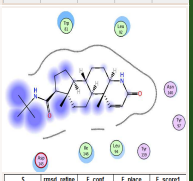
Chemotype	Flexible Alignment	Docking
		
		

Table 4. Representative hits recovered by the virtual screening protocol

CONCLUSIONS

- Compounds with potential inhibitory capabilities against bromodomains were identified.
- It is worth noting that hit structures differ from currently developed inhibitors.
- The natural products identified in this study need further testing in the search of binding modes and lead-like characterization.
- Additionally steroid scaffolds recovered here may suggest hormonal regulation in BRDs and BRDT.

Acknowledgments

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References:
[1]Prieto-Martínez F.D. et al., 2016. RSC Adv.6: 56225-56239; [2]González-Medina et al., 2016. Fut. Med. Chem. *In press*; [3]Filippakopoulos, P. et al., 2012. Bioorganic & Medicinal Chemistry. 20: 1878-1886; [4]Ferri, E., Petosa, C. & Mckenna, C.E., 2015. Biochemical Pharmacology. 106; 1-18