Finding possible mechanisms of action for the orphan drug Iobenguane I 131 using Tanimoto similarity score and Principal component analysis (PCA)

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1. Introduction

Iobenguane, or MIBG, is an aralkylguanidine analog of the adrenergic neurotransmitter norepinephrine and a radiopharmaceutical. It acts as a blocking agent for adrenergic neurons. When radiolabeled, it can be used in nuclear medicinal diagnostic techniques as well as in neuroendocrine antineoplastic treatments. It is an orphan drug, used to treat Paraganglioma.

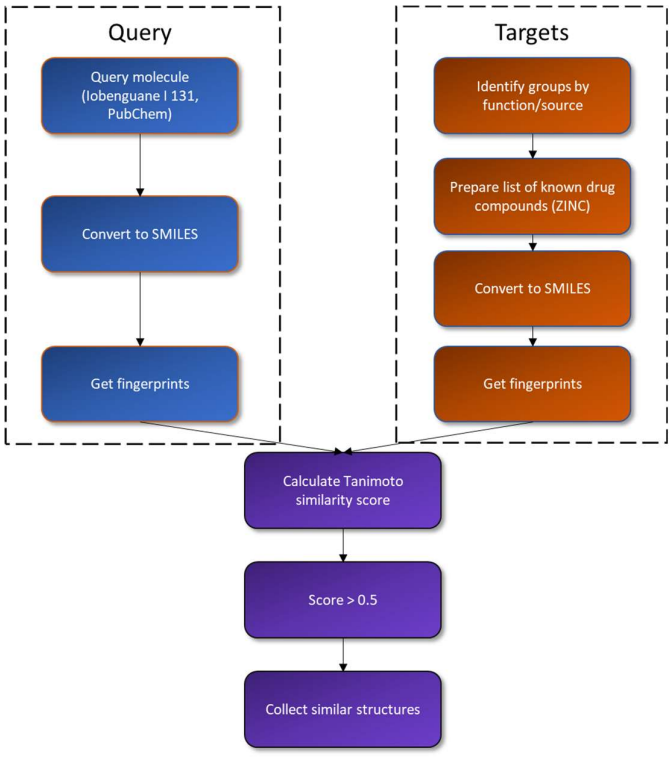
Tanimoto similarity score is a measure to calculate similarity between two chemical compounds given its fingerprints. It is a useful tool to find out similar molecules for a query molecule. Here Iobenguane I 131 is treated as the query molecule to find out possible mechanisms of action by comparing to similar molecules with known activity.

Principal Component Analysis, or PCA, is a dimensionality-reduction method that is often used to reduce the dimensionality of large data sets, by transforming a large set of variables into a smaller one that still contains most of the information in the large set. PCA is done on the query molecule and target molecule to find out hidden similarities between them.

All coding was done using Python. The molecules were obtained from the ZINC database.

2. Experimental design

2.1 Tanimoto similarity calculation



2.2 Principal component analysis

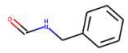
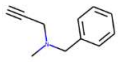
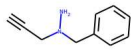
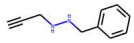
3. Results

3.1 Targets groups

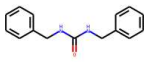
Group	Description	Sub-groups	Number of molecules identified
Biological targets	Substances/drugs that target biological molecules	Enzyme	3,10,191
		Ion channel	25,376
		Transporter	32,115
		Transcription factor	27,586
		Membrane receptors	2,17,943
Metabolites	Substances which are produced during metabolism	Primary metabolites	81,519
		Secondary metabolites	2,24,205
FDA approved	Drug substances approved by the Food and Drug Administration	Commercial	1,615

3.2 Biological targets with similarity > 0.5

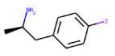
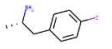
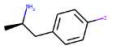
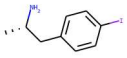
3.2.1 Enzyme targeting drugs (First 4)

ZINC ID	SMILES	Tanimoto similarity score	Molecular structure
ZINC000087515328	O=CNCc1ccccc1	0.516340	
ZINC000053084618	C#CCN(C)Cc1ccccc1	0.550898	
ZINC000026651414	C#CCN(N)Cc1ccccc1	0.522727	
ZINC000026647798	C#CCNNCc1ccccc1	0.503067	

3.2.2 Ion-channel targeting drugs

ZINC ID	SMILES	Tanimoto similarity score	Molecular structure
ZINC000000084096	O=C(NCc1ccccc1)NCc1ccccc1	0.585366	

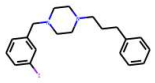
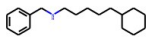
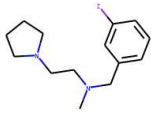
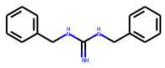
3.2.3 Transporter targeting drugs

ZINC ID	SMILES	Tanimoto similarity score	Molecular structure
ZINC000002390011	C[C@@H](N)Cc1ccc(I)cc1	0.516854	
ZINC000003619527	C[C@H](N)Cc1ccc(I)cc1	0.516854	
ZINC000002390011	C[C@@H](N)Cc1ccc(I)cc1	0.516854	
ZINC000003619527	C[C@H](N)Cc1ccc(I)cc1	0.516854	

3.2.4 Transcription factor targeting drugs

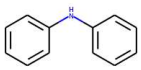
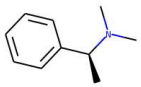
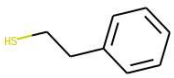
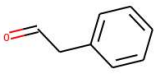
No substances with similarity > 0.5 with Iobenguane I 131

3.2.5 Membrane receptor targeting drugs (First 4)

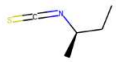
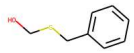
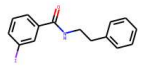
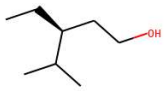
ZINC ID	SMILES	Tanimoto similarity score	Molecular structure
ZINC000029132760	Ic1cccc(CN2CCN(CCCc3ccccc3)CC2)c1	0.505155	
ZINC000013736089	c1ccc(CNCCCCCC2CCCCC2)cc1	0.535912	
ZINC000022940262	CN(CCN1CCCC1)Cc1cccc(I)c1	0.544747	
ZINC000002013275	N=C(NCc1ccccc1)NCc1ccccc1	0.721854	

3.3 Metabolites with similarity > 0.5

3.3.1 Primary metabolites (First 4)

ZINC ID	SMILES	Tanimoto similarity score	Molecular structure
ZINC000000967716	c1ccc(Nc2ccccc2)cc1	0.508929	
ZINC000002032473	C[C@@H](c1ccccc1)N(C)C	0.573964	
ZINC000004271722	SCCc1ccccc1	0.508772	
ZINC000000895323	O=CCc1ccccc1	0.513514	

3.3.2 Secondary metabolites (First 4)

ZINC ID	SMILES	Tanimoto similarity score	Molecular structure
ZINC000000167189	CC[C@@H](C)N=C=S	0.516129	
ZINC000013376404	OCSCc1ccccc1	0.513274	
ZINC000000869715	O=C(NCCc1ccccc1)c1cccc(I)c1	0.532609	
ZINC000015205244	CC[C@@H](CCO)C(C)C	0.523810	

3.4 FDA approved

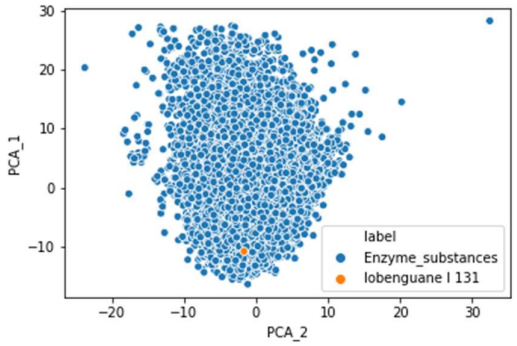
3.4.1 Purchasable

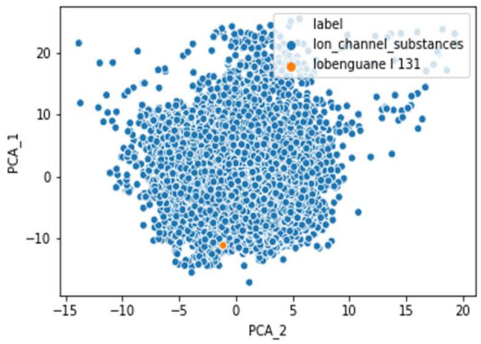
No FDA approved drug with similarity > 0.5 with Iobenguane I 131

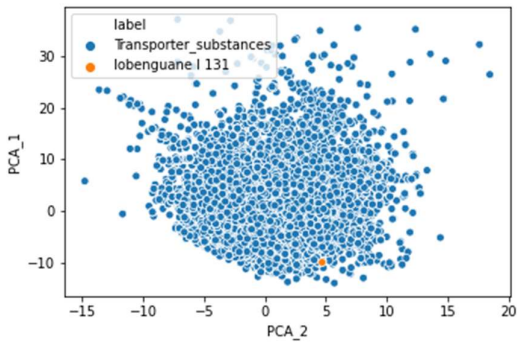
3.5 Final similarity table

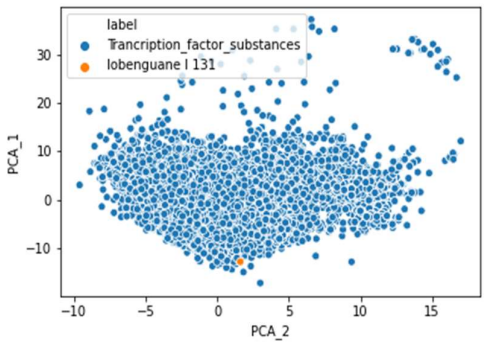
Group	Description	Sub-groups	Number of molecules with similarity > 0.5	Highest similarity score
Biological targets	Substances/drugs that target biological molecules	Enzyme	37	0.550898
		Ion channel	1	0.585366
		Transporter	4	0.516854
		Transcription factor	0	NA
		Membrane receptors	14	0.721854
Metabolites	Substances which are produced during metabolism	Primary metabolites	18	0.573964
		Secondary metabolites	8	0.537572
FDA approved	Drug substances approved by the Food and Drug Administration	Commercial	0	NA

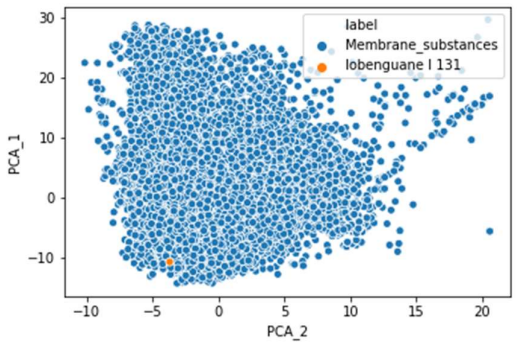
3.6 PCA plots

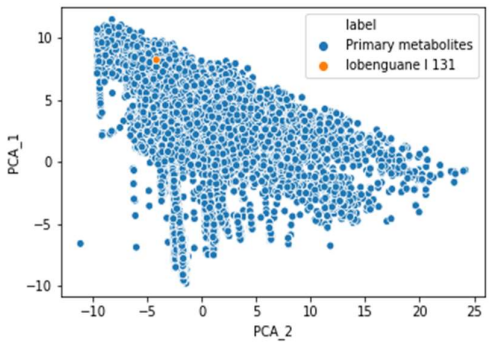

label
Enzyme_substances
Iobenguane I 131
PCA_1
PCA_2

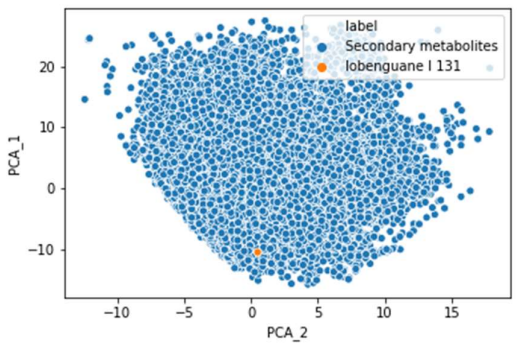

label
Ion_channel_substances
Iobenguane I 131
PCA_1
PCA_2


label
Transporter_substances
Iobenguane I 131
PCA_1
PCA_2


label
Trancription_factor_substances
Iobenguane I 131
PCA_1
PCA_2


label
Membrane_substances
Iobenguane I 131
PCA_1
PCA_2


label
Primary metabolites
Iobenguane I 131
PCA_1
PCA_2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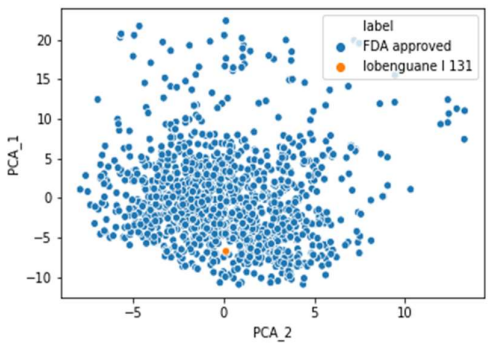
Secondary metabolites
Iobenguane I 131
PCA_1
PCA_2


label
FDA approved
Iobenguane I 131
PCA_1
PCA_2

4. Conclusion

From the Tanimoto similarity score of all the target groups in Section 3.5, it appears that query molecule Iobenguane I 131 is similar to drugs that target enzymes and membrane receptors. By looking at the PCA plots in Section 3.6, it is also evident that the query molecule is most similar to primary metabolites found in the human body and has signatures similar to FDA approved drugs. **Thus, we can conclude that the orphan drug Iobenguane I 131 is similar to a primary metabolite found in humans and it targets an enzyme or a membrane receptor.**

This is proved to be correct, as Iobenguane I 131 is similar to the neurotransmitter norepinephrine (NE), a primary metabolite that acts on membrane receptors. The method thus provides chemists with an effective way to find out the mechanism of action and/or targets of drugs whose activity is unknown.