# ARE NOVEL PSYCHOACTIVE SUBSTANCES (NPS) THAT SHARE STRUCTURAL MOTIFS WITH APPROVED COMPOUNDS MORE LIKELY TO HAVE A PSYCHOACTIVE EFFECT?

# INTRODUCTION

- ► Novel Psychoactive Substances (NPS) emerge too quickly to characterize them one-by-one in the laboratory.
- ▶ NPS are extensively discussed in online forums, providing an untapped source of data on natural experimentation.
- ▶ NPS are extensively chemically modified from their original scaffolds.
- ► It is difficult to separate fact from fiction online.

NPS listed on Wikipedia or in

with SMILES structure (n = 603)

Morgan fingerprint

literature (n = 777)

Conceptual Framework

Reports of effects of online substances are more credible if the substances share structurnal features with approved therapeutics.

RESEARCH QUESTION

What structural similarities are there between NPS and approved therapeutics?

# METHODS

Structural (Tanimoto) Similarity

Cluster to Identify Shared Motifs (Figure 1)

Types of Substances in Each Cluster (Figure 2)

Figure 1: Study design.

**Morgan Fingerprint** All fragments of a molecule up to 4 molecules in length

**Tanimoto Similarity** Fraction of Morgan fingerprints that two molecules share

Hierarchical Clustering Group substances together based on their Tanimoto similarities. Substances within a group have higher similarity to each other than to any substance not in the group.

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RESULTS



Figure 2: Structural Similarity of Novel Psychoactive Substances & Approved **Compounds.** X- and y-axes show names of substances. Only ever  $3^{rd}$  name shown for sake of space. Darkness of each square in represents the structural similarity of the compounds indicated by the x- and y-axes. Colorbar in upper left shows scale for structural similarity. Row and column dendrograms indicate groups of structurally similar compounds.



Figure 3: Type of Substances in Each Cluster. X-axis shows cluster number. Y-axis shows the fraction of substances in each cluster that are FDA-approved.

	Cluster		
	1	FDA	Sodium nitrite, carbonate
		NPS	1,4-butanediol
	2	FDA	acamprosate ca acetrizoate sodi
<ul> <li>mesna</li> <li>potassium citrate</li> <li>helium</li> <li>disulfiram</li> <li>acetylcholine chloride</li> <li>dezocine</li> <li>lefamulin acetate</li> <li>prednisolone acetate</li> <li>Drostanolone</li> </ul>		NPS	1,3-dimethylbut aminoisobutyric etam, pramirace
<ul> <li>erythromycin lactobionate</li> <li>insulin degludec</li> <li>bremelanotide acetate</li> <li>cefotiam hydrochloride</li> <li>gefitinib</li> <li>quinidine polygalacturonate</li> <li>fludarabine phosphate</li> <li>chlormezanone</li> <li>Adinazolam</li> </ul>	3	FDA	oxymorphone, e fluorometholone
<ul> <li>Mebroqualone</li> <li>ethotoin</li> <li>AM-1235</li> <li>5F-CUMYL-PINACA</li> <li>amprenavir</li> <li>benztropine mesylate</li> <li>imipramine pamoate</li> </ul>		NPS	DOC, Tetrahyd prostanozol, me
<ul> <li>Methoxypiperamide</li> <li>irbesartan</li> <li>ubrogepant</li> <li>cidofovir</li> <li>safinamide mesylate</li> <li>phentermine hydrochloride</li> <li>warfarin potassium</li> <li>Methylenedioxypyrrolidinohexiophenone</li> </ul>	4	FDA NPS	abaloparatide, h BPC-157, GHR
<ul> <li>- epinephrine</li> <li>- diclofenac sodium</li> <li>- bitolterol mesylate</li> <li>- methyldopa</li> <li>- mesalamine</li> <li>- 5-MeO-DET</li> <li>- betazole hydrochloride</li> </ul>	5	FDA	abacavir, entre cefmetazole, iofe
U-49900 - olaparib - olaparib - orzenoxacin - Vitamin B9 - Vitamin B9 - piroxicam - mirabegron - Ethylone - albuterol - albuterol - albuterol - shydrochloride - albuterol - albuterol - state disodium - albuterol - state disodium - albuterol - state disodium - albuterol		NPS	1P-ETH-LAD, fluoromethcathi ipradrol, mepry
dronedarone pelennamine gadox aminosal rilpivirine	Table 1: Drug Ad	Examp ministra	le members of each ation. NPS, novel pa

- synthetic CB 1 agonistt
- and the most NPS.
- from side chain modification.
- approaches.



### Example Substances

gallium-67 citrate, talc, sodium thiosulfate, magnesium

alcium, acetazolamide, acetic acid, acetohydroxamic acid, ium, alprostadil, misoprostol, iotrolan

ylamine, 2-methyl-2-butanol, 2-methyl-2-pentanol, 3acid BOB, MET, methylhexanamine, oxiracetam, piracetam

estramustine, dextromethorphan, paricalcitol, ulipristal,

lrogestrinone, metribolone, dimethyltrienolone, trestolone, ethasterone, clostebol, HU-308, metenolone enanthate

histrelin, bilvarudin, gonadorelin, goserelin P-2, examorelin, tesamorelin, examorelin, melanotan

ctinib, aripiprazole, phenelzine, mitotane, bumetanide, exidine

4-chlorobutylcathinone, MDA-19, isoproscaline, 4inone, 5-methoxymethylone, PTI-2, AB-PICA, desoxypvlcaine, 5F-AMB

cluster. FDA, substances approved by the United States Food & psychoactive substances. LAD, lysergic acid diethylamide, BOB, beta-methoxy-2C-B., MET, methyltryptamine, DOC, 2,5-dimethoxy-4-chloroamphetamine, MDA-19,

## CONCLUSIONS

► Computational methods can identify similarities between the two-dimensional structures of novel psychoactive substances and substances approved by the FDA for medical use. Cluster 5 contained the most FDA-approved psychoactive substances

► Computational methods can identify structural similarities between NPS and drugs that are not psychoactive, providing a way to predict additional effects that arise

## LIMITATIONS

► Our conclusions are limited by the approximation of chemicals achiral structures with no distinguishing 3D features or resonance structures.

► We did not assess the fraction of NPS compounds in clusters with FDA-approved compounds that were known not to be psychoactive in the amounts usually consumed. Nor did we compare the performance of our algorithm to other