Are novel psychoactive substances (NPS) that share structural motifs with approved compounds more likely to have a psychoactive effect?

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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.

Conceptual Framework

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

Research Question

What structural similarities are there between NPS and approved therapeutics?

Methods

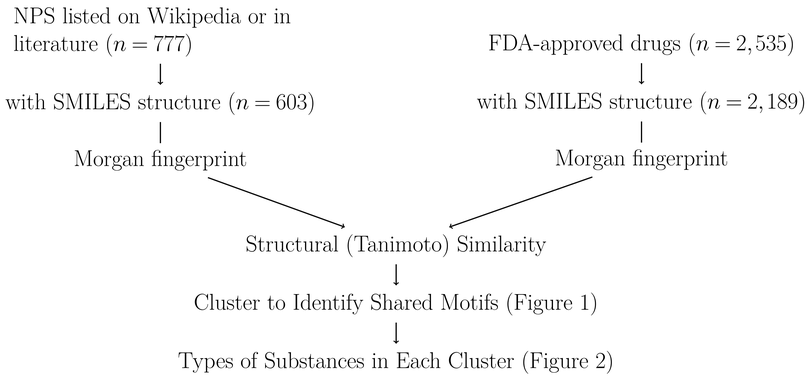

Figure 1: **Study design.**

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.

Acknowledgments

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Results

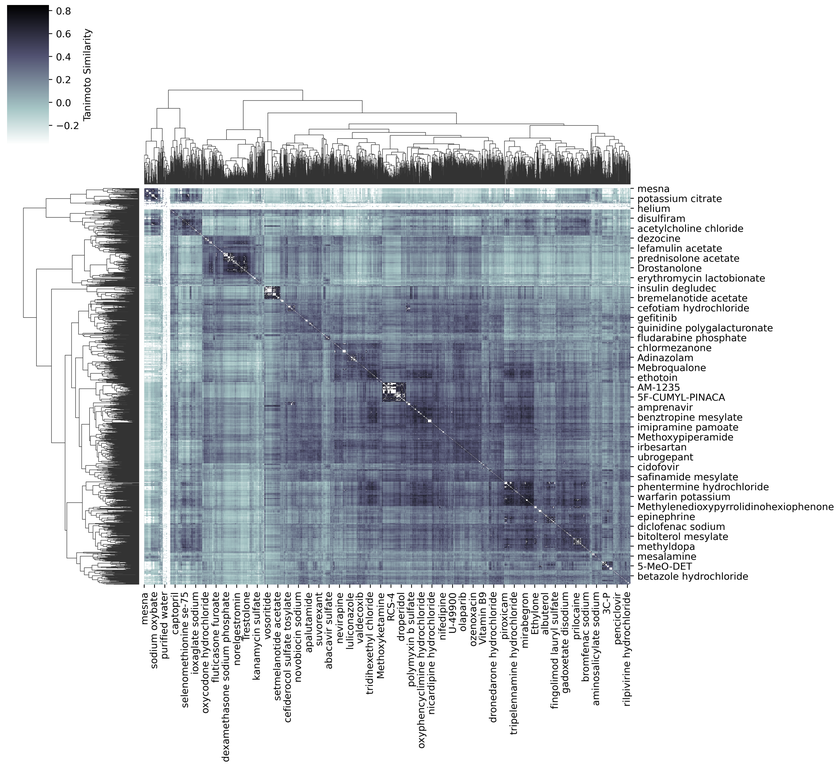

Figure 2: **Structural Similarity of Novel Psychoactive Substances & Approved Compounds.** X- and y-axes show names of substances. Only ever 3^{rd} name shown for sake of space. Darkness of each square in represents the structural similarity of the compounds indicated by the x- and y-axes. Colorbar in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

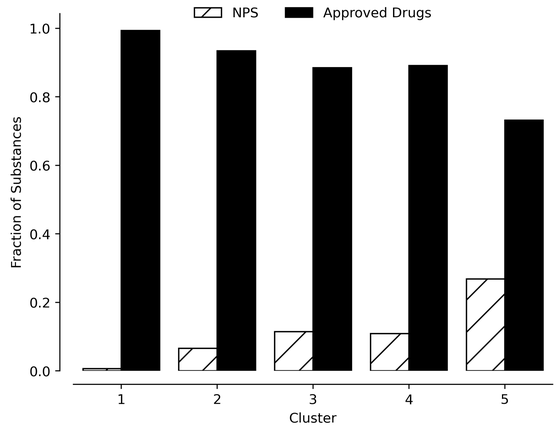

Figure 3: **Type of Substances in Each Cluster.** X-axis shows cluster number. Y-axis shows the fraction of substances in each cluster that are FDA-approved.

Cluster		Example Substances
1	FDA	Sodium nitrite, gallium-67 citrate, talc, sodium thiosulfate, magnesium carbonate
	NPS	1,4-butanediol
2	FDA	acamprosate calcium, acetazolamide, acetic acid, acetohydroxamic acid, acetrizoate sodium, alprostadil, misoprostol, iotrolan
	NPS	1,3-dimethylbutylamine, 2-methyl-2-butanol, 2-methyl-2-pentanol, 3-aminoisobutyric acid BOB, MET, methylhexanamine, oxiracetam, piracetam, pramiracetam
3	FDA	oxymorphone, estramustine, dextromethorphan, paricalcitol, ulipristal, fluorometholone
	NPS	DOC, Tetrahydrogestrinone, metribolone, dimethyltrienolone, trestolone, prostanozol, methasterone, clostebol, HU-308, metenolone enanthate
4	FDA	abaloparatide, histrelin, bilvarudin, gonadorelin, goserelin
	NPS	BPC-157, GHRP-2, examorelin, tesamorelin, examorelin, melanotan
5	FDA	abacavir, entrectinib, aripiprazole, phenelzine, mitotane, bumetanide, cefmetazole, iofexidine
	NPS	1P-ETH-LAD, 4-chlorobutylcathinone, MDA-19, isoproscaline, 4-fluoromethcathinone, 5-methoxymethylone, PTI-2, AB-PICA, desoxypipradrol, meprylcaine, 5F-AMB

Table 1: Example members of each cluster. FDA, substances approved by the United States Food & Drug Administration. NPS, novel psychoactive substances. LAD, lysergic acid diethylamide, BOB, *beta*-methoxy-2C-B., MET, methyltryptamine, DOC, 2,5-dimethoxy-4-chloroamphetamine, MDA-19, synthetic CB_1 agonistt

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 and the most NPS.
- Computational methods can identify structural similarities between NPS and drugs that are not psychoactive, providing a way to predict additional effects that arise from side chain modification.

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 approaches.