Improving the Understanding of Anti-Epileptic Drugs

Using Quantitative Structure Activity Relationships

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Background

Epilepsy

- One of the more common neurological conditions
- Recurrent, unprovoked seizures
- Affects about 65 million people around the world (3 million in the U.S.)

Issues with Current Treatments

- Do not fully block seizure (epileptogenic) activity in all patients
- Levels often prescribed in toxic range to properly control brain activity causing unwanted symptoms

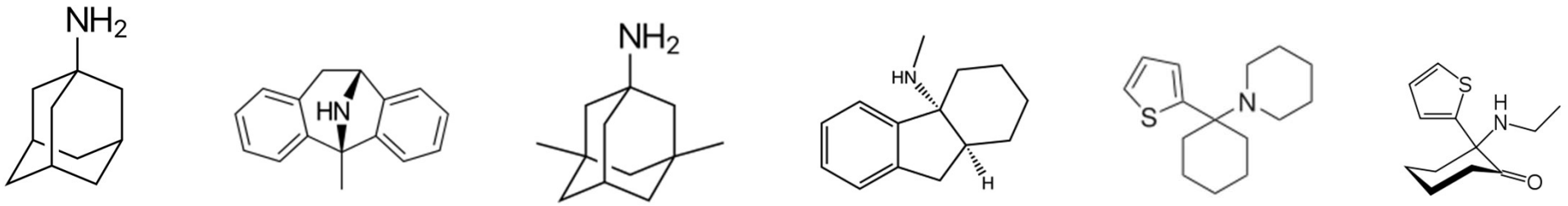
Gaps in Current Approaches

- The research and development of new medicines is expensive and time consuming
- There is a need for a better way to identify promising chemicals and narrow the testing pool

Background (contd.)

Quantitative Structure Activity Relationships (QSARs)

- Using the physicochemical properties of chemicals with similar structures (training set) to make predictive models for similarly structured chemicals (test sets)
  - Narrows down chemicals to be researched for development
  - Predict environmental consequences based on known structural effects

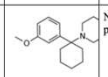
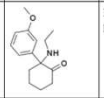
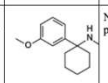
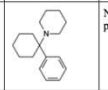
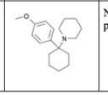


Similar structures from our chemical search

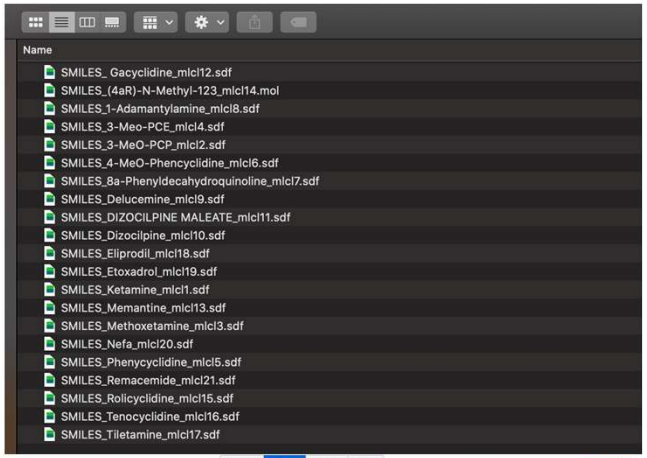
Methods/Experimental Setup

Noncompetitive NMDA Antagonists

- Anticonvulsants
- Decrease excitatory amino acid release
- Treatment of epilepsy
- Current research into preventative implications in Alzheimer's and Parkinson's disease

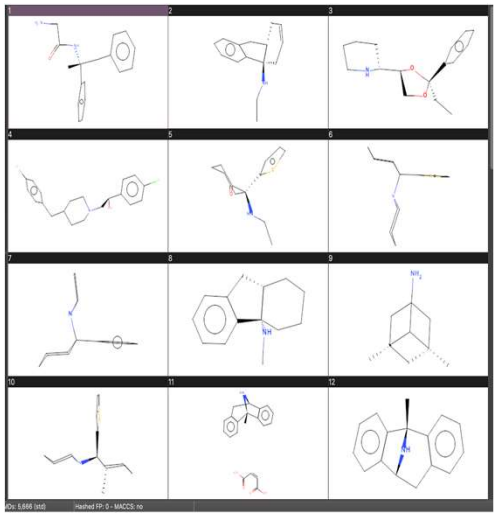
Drug	Structure	Expected Mechanism		SMILE	LD50	mol/kg
(RS)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone Ketamine		Noncomp	All very similar compounds with the same mechanism given some are analogs of each other.	CNC1(CCCCC1=O)c2ccccc2Cl	600 mg/kg	0.00252
3-Methoxyphencyclidine 3-MeO-PCP		Noncomp		COc1cccc(c1)C2(CCCCC2)N3CCCCC3	~100 mg/kg	0.000365737
R/S)-2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexanone Methoxetamine		Noncomp		CCNC1(CCCCC1=O)c2cccc(c2)OC	~280 mg/kg	0.001132
N-Ethyl-1-(3-methoxyphenyl)cyclohexan-1-amine 3-Meo-PCE		Noncomp		CCNC1(CCCCC1)c2cccc(c2)OC	~100 mg/kg	0.0004285
1-(1-Phenylcyclohexyl)piperidine Phencyclidine		Noncomp		c1ccc(cc1)C2(CCCCC2)N3CCCCC3	~57 muMoles/kg	0.000057
1-[1-(4-methoxyphenyl)cyclohexyl]-piperidine 4-MeO-Phencyclidine		Noncomp		COC1=CC=C(C=C1)C2(CCCCC2)N3CCCCC3	~1000 mg/kg	0.003657

Create group of chemicals with similar features/mechanisms



Download files containing 3D chemical structural information

Methods/Experimental Setup (contd.)



Upload into descriptor calculating software

Calculate Chemical Descriptors (Molecular weight, hydrophobicity, etc.)

Chemical name	LD50	Chemical name	LD50 (mol/kg)
Ketamine	0.00252	Dizoclipine	0.0000898
3-MeO-PCP	0.000365737	Memantine	0.0015186
Methoxetamine	0.001132	(4aR)-N-Methyl-1,2,3,4,9,9a-hexahydro-4aH-fluoren-4a-amine	0.0000994
3-Meo-PCE	0.0004285	Rolicyclidine	3.3265
Phencyclidine	0.000057	1-(1-(2-Thienyl)cyclohexyl)piperidine	3.1153
4-MeO-Phencyclidine	0.003657	Tiletamine	0.021037
Amantadine	0.0001889	Etoxadrol	0.000876
NEFA	0.0016018	Remacemide	0.0033538

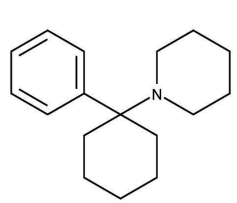
Input information about chosen end point

Current Status

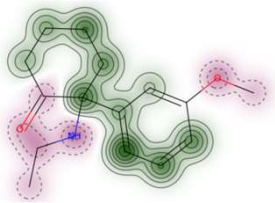
- Creating the model using machine learning
- Validation- analyzing prediction precision
  - R-squared value
  - Improves with additional data (molecular structures) added

Supplemental Information

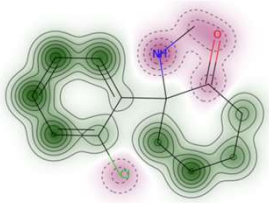
```
from rdkit import Chem
mol = Chem.MolFromSmiles('CNC1(CCCCC1=O)c2ccccc2Cl')
refmol = Chem.MolFromSmiles('c1ccc(cc1)C2(CCCCC2)N3CCCCC3')

from rdkit.Chem import Draw
from rdkit.Chem.Draw import SimilarityMaps
fp = SimilarityMaps.GetAPFingerprint(mol, fpType='normal')
fp = SimilarityMaps.GetTTFingerprint(mol, fpType='normal')
fp = SimilarityMaps.GetMorganFingerprint(mol, fpType='bv')

fig, maxweight = SimilarityMaps.GetSimilarityMapForFingerprint(refmol, mol, SimilarityMaps.GetMorganFingerprint)
```



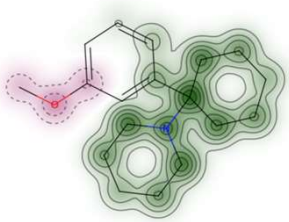
Reference Molecule Phencyclidine



Methoxetamine



Ketamine



3-MeO-PCP

- Similarity maps - RDkit in Python
- Green – similarity decreases if this feature is removed
- Pink – no change in similarity if this feature is removed

Discussion/Next Steps

- Continue to add more data points to increase predictability of the model
- Find negative controls for machine learning
  - Molecule with similar structure and no NMDA activity
  - Molecule with negligible toxicity
- Endpoint: accurately predict Lethal Dose 50 values for similarly structured substances not included in the training set

Conclusions

- QSARs are very useful in predicting activity of molecules
- It is important to have enough similar molecular structures to create an accurate model
- QSARs must be created using readily available values for endpoint goal (binding affinity, toxicity, etc.)
- QSARs are not always reliable, they are most useful for screening and narrowing down chemicals for further research

What benefits did you get from your SURE experience?

- The opportunity to be a functioning member of a team
- Introductory knowledge of pharmacokinetics and pharmacodynamics
- Familiarity with the steps involved in creating a Quantitative Structure – Activity Relationship model from scratch
- Experience installing and navigating various computer software
- Understanding how to search databases to collect relevant information

References & Acknowledgements

[1] Jensen, Jan. “Introduction to RDKit Part 1.” *YouTube*, YouTube, 5 Nov. 2019, www.youtube.com/watch?v=ERvUf_lNopo.

[2] Mauri, A. (2020). alvaDesc: A tool to calculate and analyze molecular descriptors and fingerprints. In K. Roy (Ed.), Ecotoxicological QSARs (pp. 801–820). Humana Press Inc.

[3] Riniker, S.; Landrum, G. A. “Similarity Maps - A Visualization Strategy for Molecular Fingerprints and Machine-Learning Methods” *J. Cheminf.* **5**:43 (2013).

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Thank you

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