Chemical space of tetra-peptides and cyclic peptides for drug discovery

Mariana González-Medina,[1] Fernando D. Prieto-Martínez,[1] Oscar Méndez-Lucio,[1] Richard A. Houghten,[2] José L. Medina-Franco[1]*

[1]Facultad de Química, Departamento de Farmacia, Universidad Nacional Autónoma de México, Avenida Universidad 3000, Mexico City 04510, México

[2]Torrey Pines Institute for Molecular Studies, 11350 SW Village Parkway, Port St. Lucie, FL 34987, USA

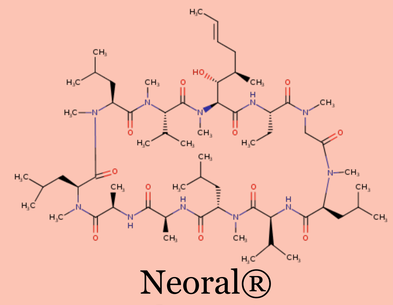
mgm_14392@comunidad.unam.mx, medinajl@unam.mx

Why peptides?

Recent discoveries on how diseases develop have led to the identification of novel target classes. However, traditional small or "drug like" compounds have not been successful addressing these "difficult to drug" targets.

New approaches are required, **drug discovery needs to explore beyond the Ro5 chemical space!**

Recently, peptides have appeared as starting points for the discovery of beyond the Ro5 compounds with therapeutic applications, particularly for metabolic diseases and oncology. This is no surprise, since peptides control all aspects of cellular function and intercellular communication. In addition, peptides offer a broad range of chemical diversity and are selective to specific targets [1,2].



Neoral®
Cyclosporin A
Oral administration

Goal

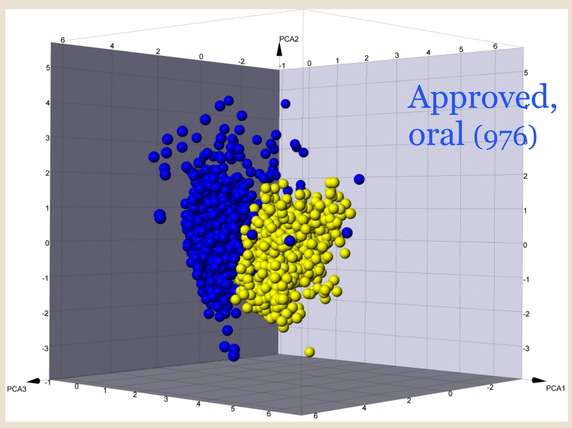
Compare the chemical space of cyclic and tetra-peptides to the chemical space of compounds in MLSMR approved drugs with oral and parenteral administration.

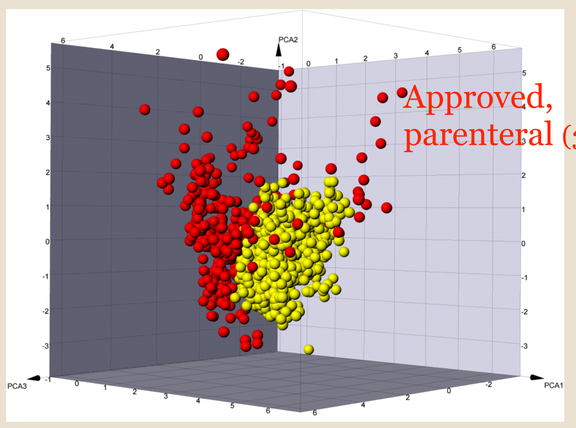
Methodology

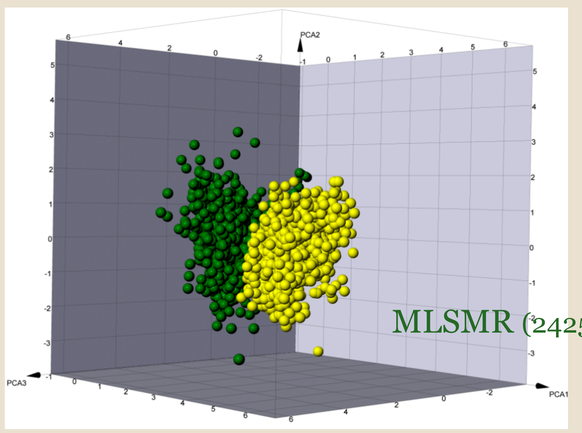
Chemical space, with principal component analysis (PCA) of six molecular properties and logistic PCA with MACCS keys (166-bits) fingerprints.

Results

PCA with molecular properties, tetra-peptides (1003)



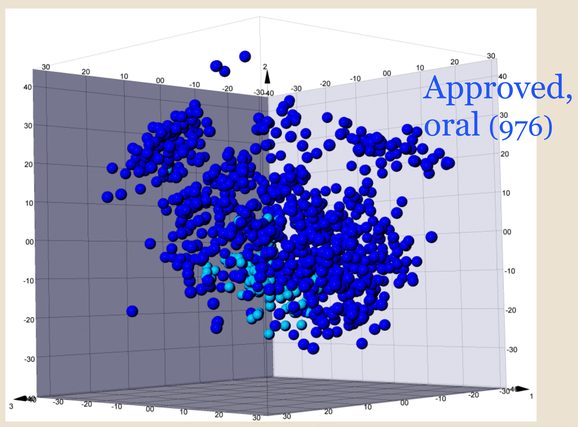


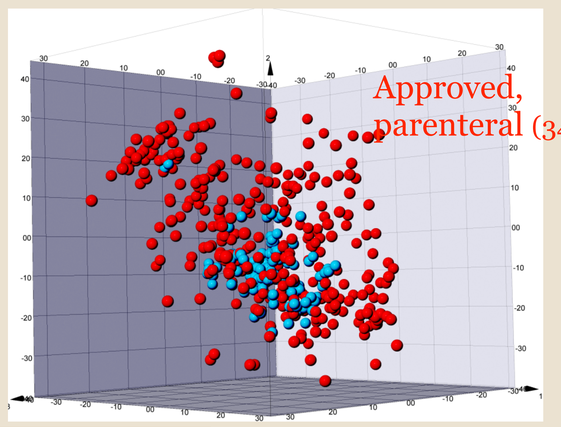


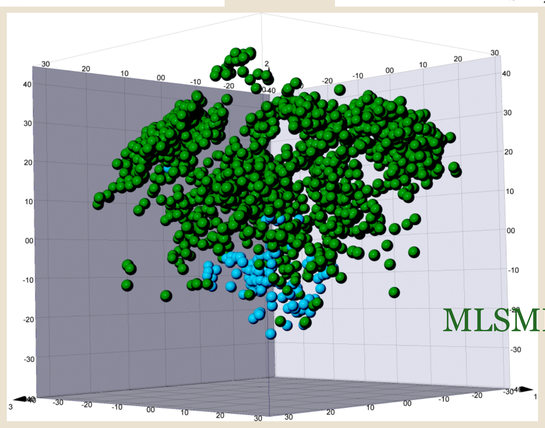
The first 3 PCs retrieved 97.7% of the variance.

- MW had the highest contribution to the first PC.
- RTB had the highest contribution to the second PC.
- PSA had the highest contribution to the third PC.

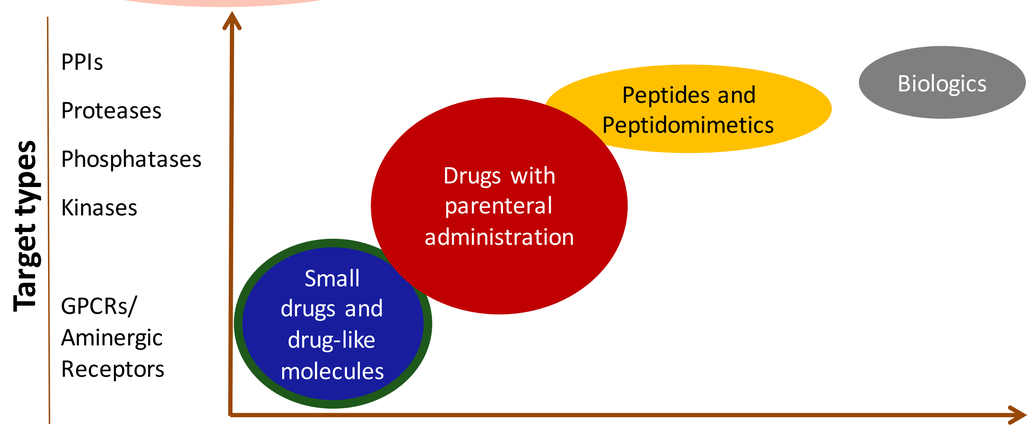
Logistic PCA with MACCS keys (166 bits) fingerprints, Cyclic peptides



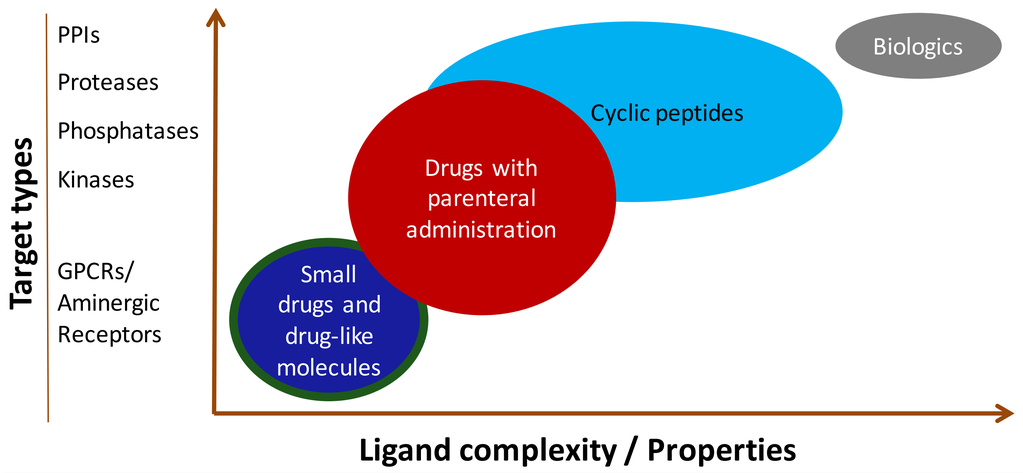




Conclusions



Tetra-peptides are less diverse and therefore more clustered, forming a highly dense library. Most tetra-peptides occupy a different region of the approved drugs chemical space.



Cyclic peptides are more diverse and scattered in the chemical space, covering regions of the chemical space of approved drugs.

Perspectives

- Expand the study to data sets containing peptides with more amino acids (e.g. hexapeptides, etc) and analyze their chemical space.
- Create data sets with cyclic peptides containing a specific number of amino acids and analyze their chemical space.

Acknowledgments

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References

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