Design of Novel Inhibitors for the Aldehyde Dehydrogenases

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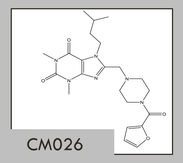
BACKGROUND

- Dopaminergic ligands, known as the 'LP series' may behave as inhibitors for aldehyde dehydrogenases (ALDH), an enzyme that is involved a series of enzymes that cause the deactivation of dopamine derived from L-DOPA.
- ALDH is also associated with the conversion of al-trans-retinal to al-trans-retinoic acid. Retinoic acid deficiency is associated with Parkinson's and impairs vestibular functions. [1]
- ALDH-1A1 enzyme is associated with cancer, obesity, and cataracts.
- Knowing how the intermolecular forces between ALDH and the LP series is important for drug design.
- The targeted inhibition of the ALDH enzyme may help to prolong the effectiveness of L-DOPA, resulting in a net increase in pharmacological efficiency for L-DOPA.
- Our research is based off of the previously tested inhibitor CM026. CM026 has a good potency for ALDH1A1 but has sterically hindering R-groups on the xanthine ring. [2]
  - CM026 selectivity was largely determined by GLY 458. [3]

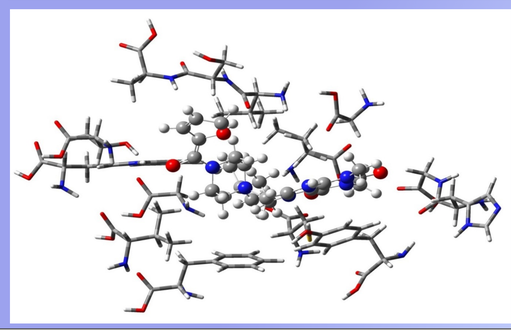
COMPUTATIONAL METHODS

- **Crystal structure**: Retrieved from Protein Data Bank (4WP7)
- **Optimization**:
  - Complex optimized using M062X/6-31G[4,5]
- **Interaction Energies**:
  - Counterpoise corrected interaction energies
  - M062X with 6-311+G* basis set[4,5]
- **Solvation**: Implicit solvation using Polarizable Continuum Model[6] (water as solvent)

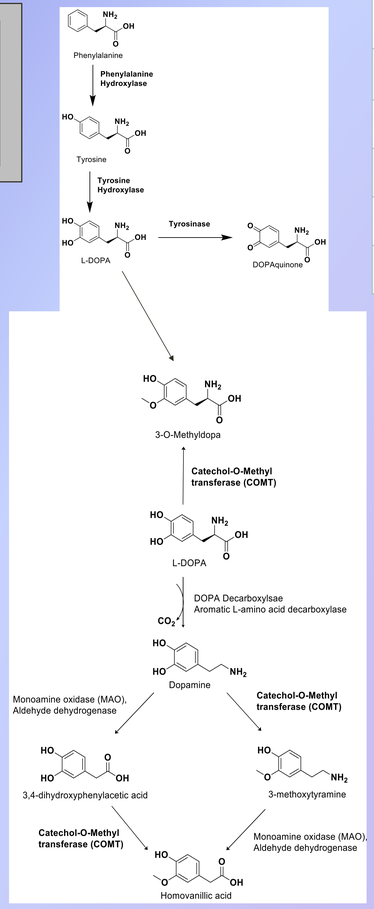


CM026

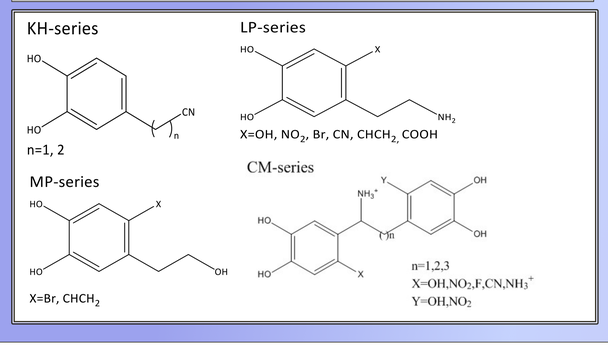
ALDH with Inhibitor



Biosynthetic pathway

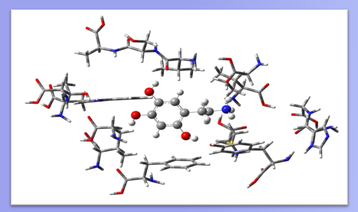


Dopaminergic Derivatives

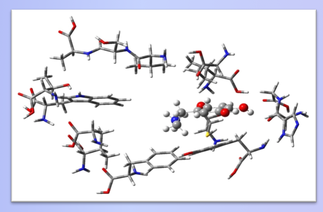


- Below are three different orientations of the dopaminergic derivatives, also known as the LP series. "A" and "B" orientation have one LP in the active site as for "O" orientation has two LP's in the active site.
- These orientations are tested to decipher which has the highest total interaction energy, when comparing the energy to the model inhibitor.

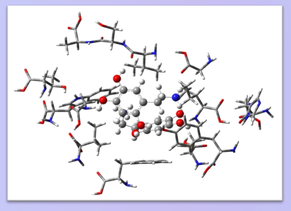
LP1 "A" Orientation



LP1 "B" Orientation



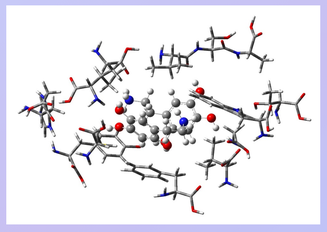
2LP1 "O orientation



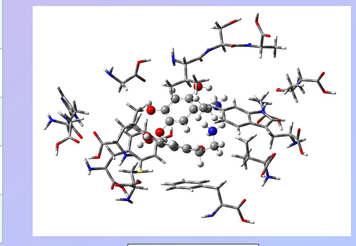
COMPARISON OF INTERACTION ENERGIES (kcal/mol)

Inhibitor	Single Molecule IE (kcals)	Double Molecule IE (kcals)
LP-OH	-53.0 (B)	-126.0 (A & B)
LP-Cyclic	-36.7 (B)	NA
LP-NO2	-48.0 (B)	-135.8 (B)
LP-Br	-47.2 (B)	-141.9 (A)
LP-CN	-47.5 (B)	-129.6 (O)
LP-CHCH2	-48.4 (B)	-118.9 (O)
LP-COO-	-121.1(A)	NA
KH-H	~19.7 (A)	-49.5 (O)
KH (n=1)	-20.6 (B)	-46.3 (B)
KH (n=2)	-21.3 (B)	NA
KH (n=3)	-28.6 (B)	NA

- Two of the 6-hydroxydopamines in the "O" and "A" orientation are shown to fit inside the active site resulting in a much smaller interaction energy.



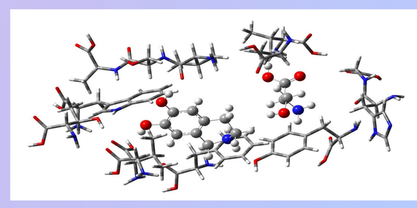
"O" orientation



"A" orientation

COMPARISON OF INTERACTION ENERGIES (kcal/mol)
Common mutations in active site

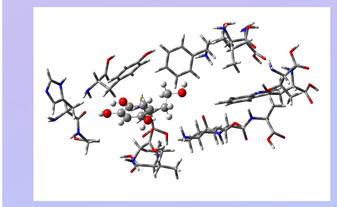
Inhibitor	CS	G125S	V460T
Cyclic dopamine (B orientation)	-35.7	-35.7	-32.3



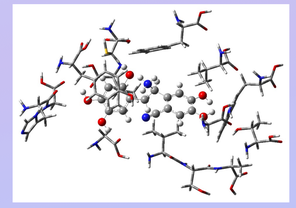
- Mutation Cysteine to Serine in ALDH active site with LP2 "B" Orientation

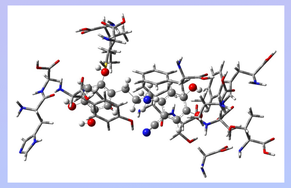
CM and MP SERIES IN ALDH ACTIVE SITE

- The CM series are combined version of the two dopaminergic derivatives creating a larger inhibitor in the active site.
- The NH_3^+ on the derivatives is now an OH tail on the MP series.



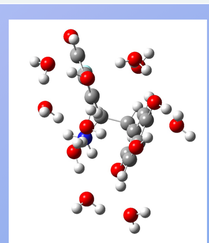
- Mp1 is the small inhibitor in this active site resulting in an even smaller interaction energy compared to the LP's.





- Above we have the CM series, starting with CM151 and CM251.

Inhibitor	Total IE (kcals)
MP1	-24.3
MP2	-18.6
MP3	-23.7
CM1	-76.8
CM211	-70.1
CM131	-82.5
CM231	-76.6
CM241	-79.7
CM151	-87.5
CM251	-94.9



- During the desolvation process, the CM molecules spend more energy on unfolding in the ALDH active site.
- This results in an overall energy penalty for unfolding.
- Pictured is the CM molecule folded before entering ALDH.

CONCLUSION

- 6-carboxydopamine (A orientation) and 6-hydroxydopamine, 6-nitrodopamine, 6-ethenyldopamine (B orientation) have the highest total interaction energy, closest to the modeled inhibitor, CM026.
- With 2 'LPs' in the active site, the "A" and "B" orientation are equally more favorable than the "O" orientation.
- With '2LPs' in the active site that are more neutral , these are more favored.
- Binding in the active site with mutations such as Cysteine to Serine, Glycine to Serine, and Valine to Threonine, does not significantly change the binding energy, supporting that the ligand would be viable to bind with these mutations.
- The active site is favoring longer molecules such as the CM series and 2 'LPs' in the active site as for the LP and MP series.
- M062X provided consistent results with LP2 in previous work with our research group.[7]
- The CM series is to be more promising than the original CM026 in the ALDH active site because of the interaction energies.

REFERENCES

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