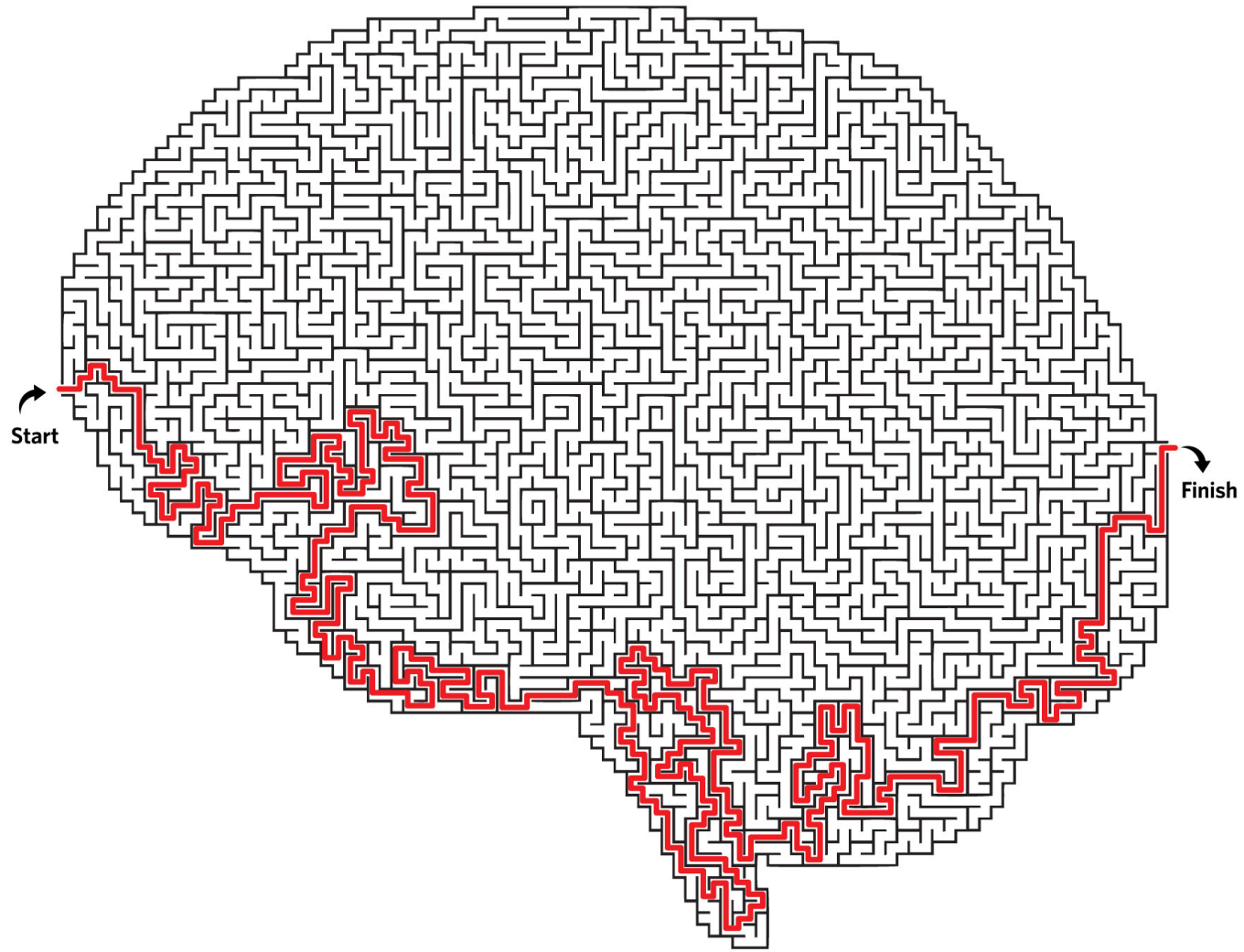




COMPUTATIONAL INSIGHT INTO THE MAO B ENZYME IRREVERSIBLE INHIBITION



Tana Tandarić
Computational Chemistry and Biochemistry group
Ruđer Bošković Institute

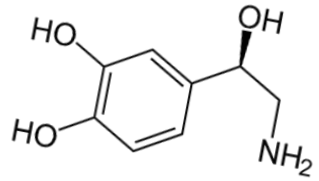




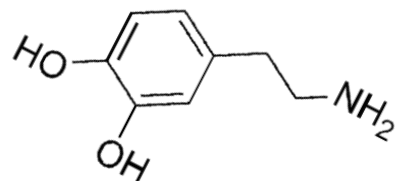
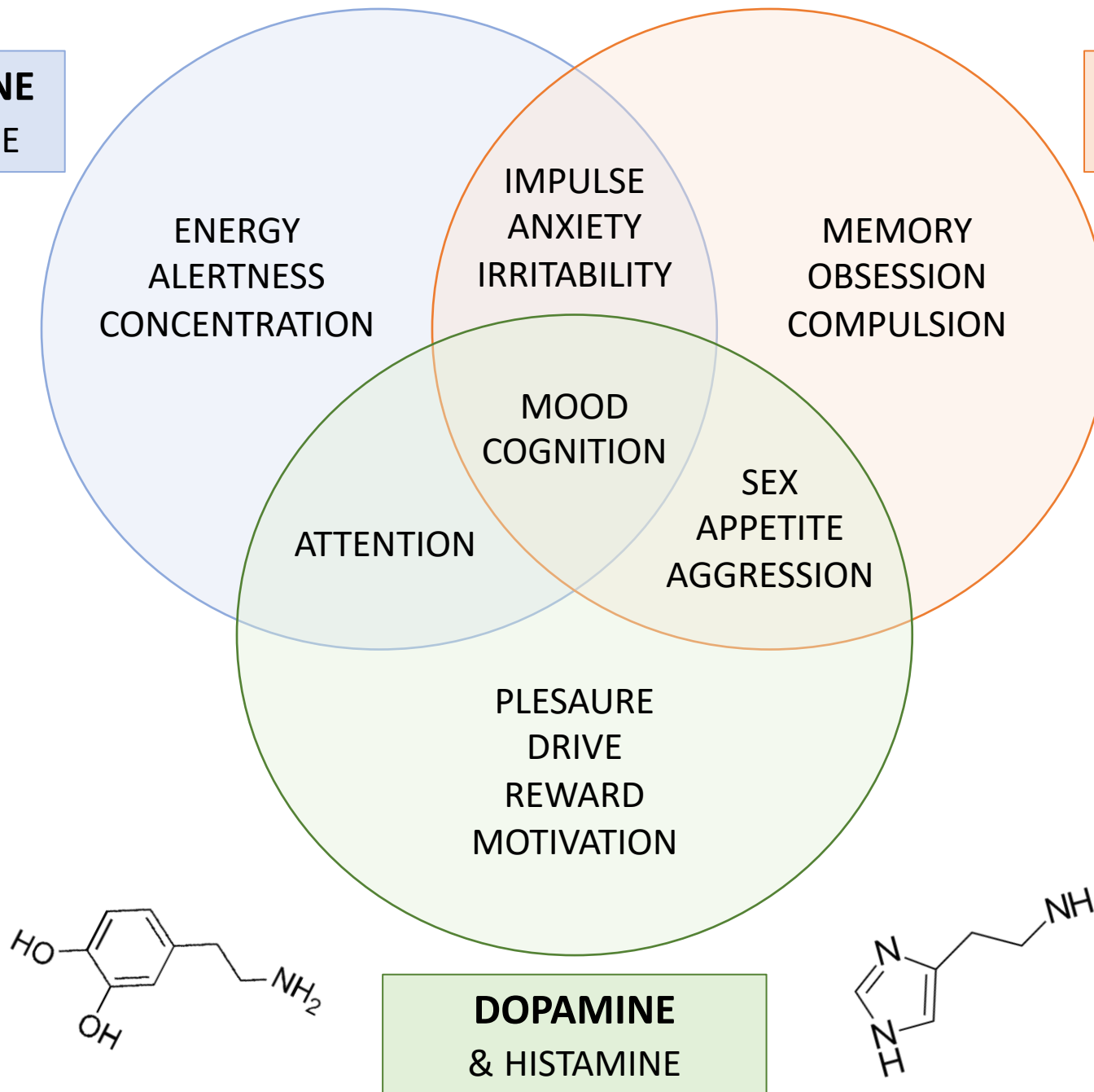
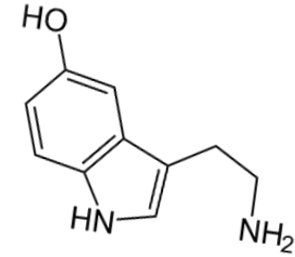
- 300 million people worldwide are suffering from depression
- 800,000 people commit suicide in one year
- 50 million people have some form of dementia, 10 million new cases a year
- 25% of the world's population has some form of mental disorder
- 2.5 trillion dollars is the global annual cost of treating mental disorders



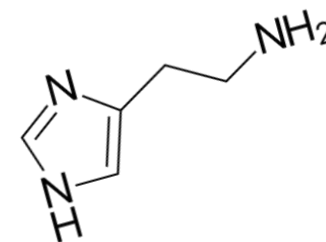
**NOREPINEPHRINE
& ACETYLCHOLINE**

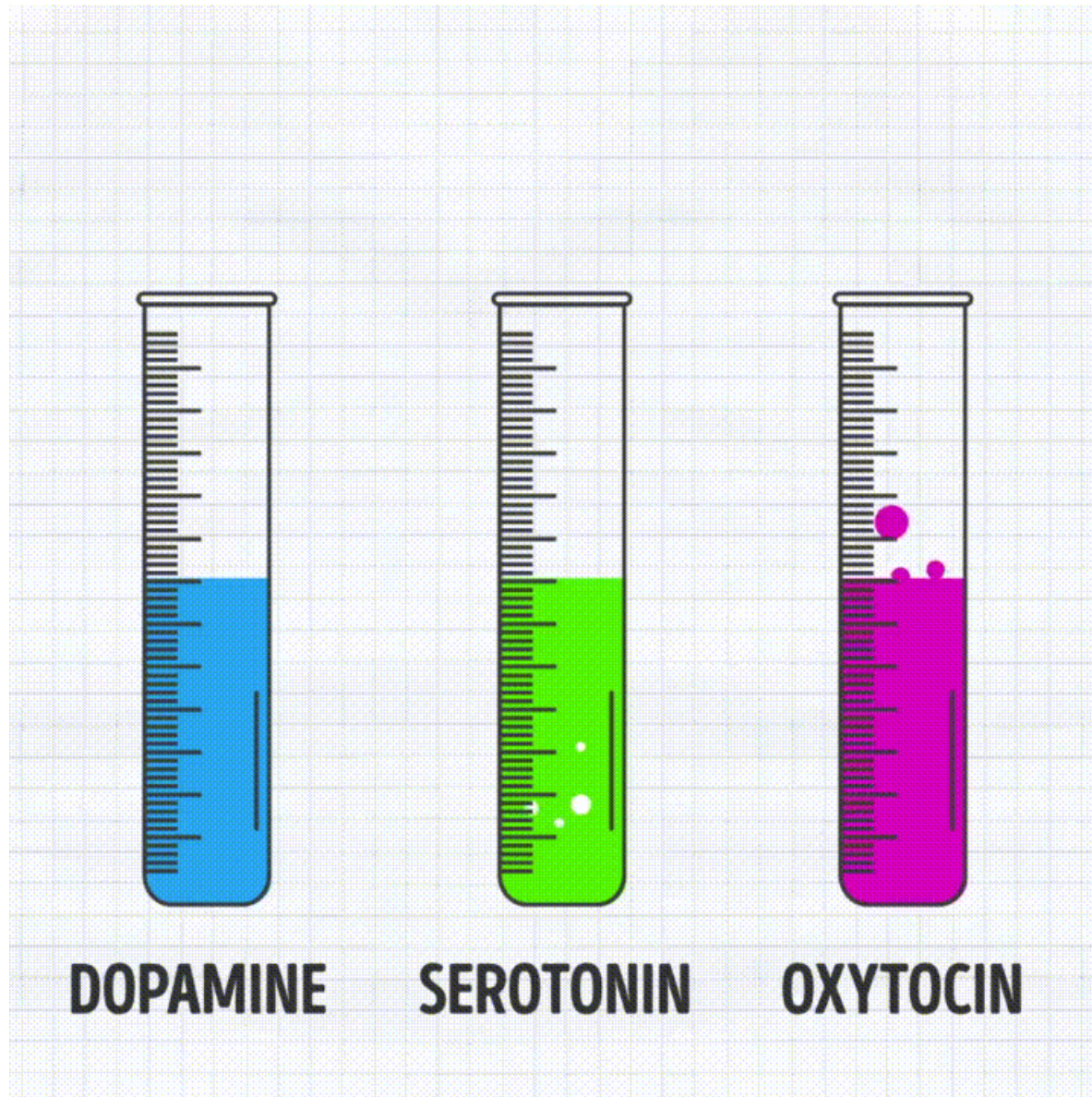


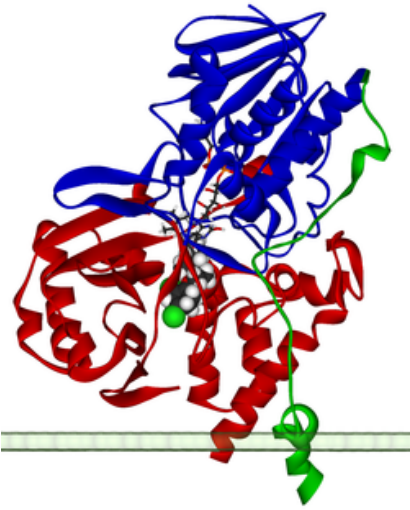
**SEROTONINE
& GLUTAMINE**



**DOPAMINE
& HISTAMINE**





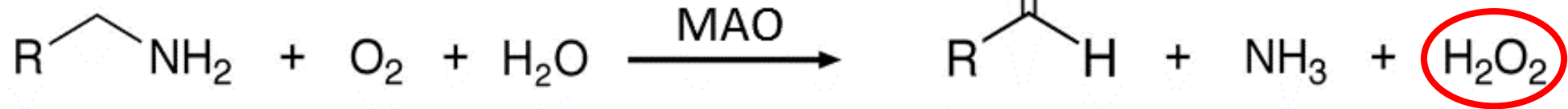
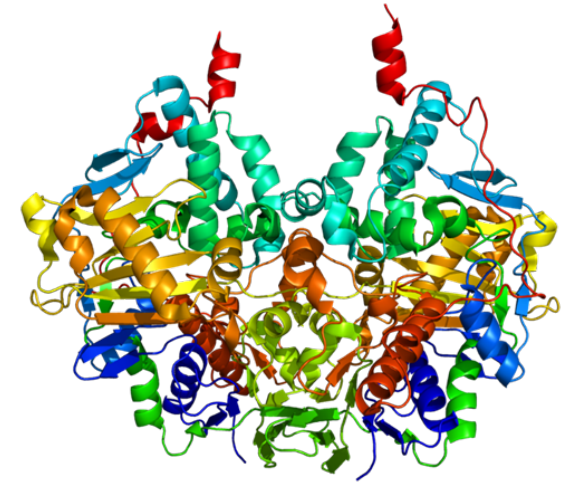


MAO A

- Depression
- Anxiety disorders
- Antisocial behavior

MAO B

- Parkinson's Disease
- Alzheimer's disease (AD)



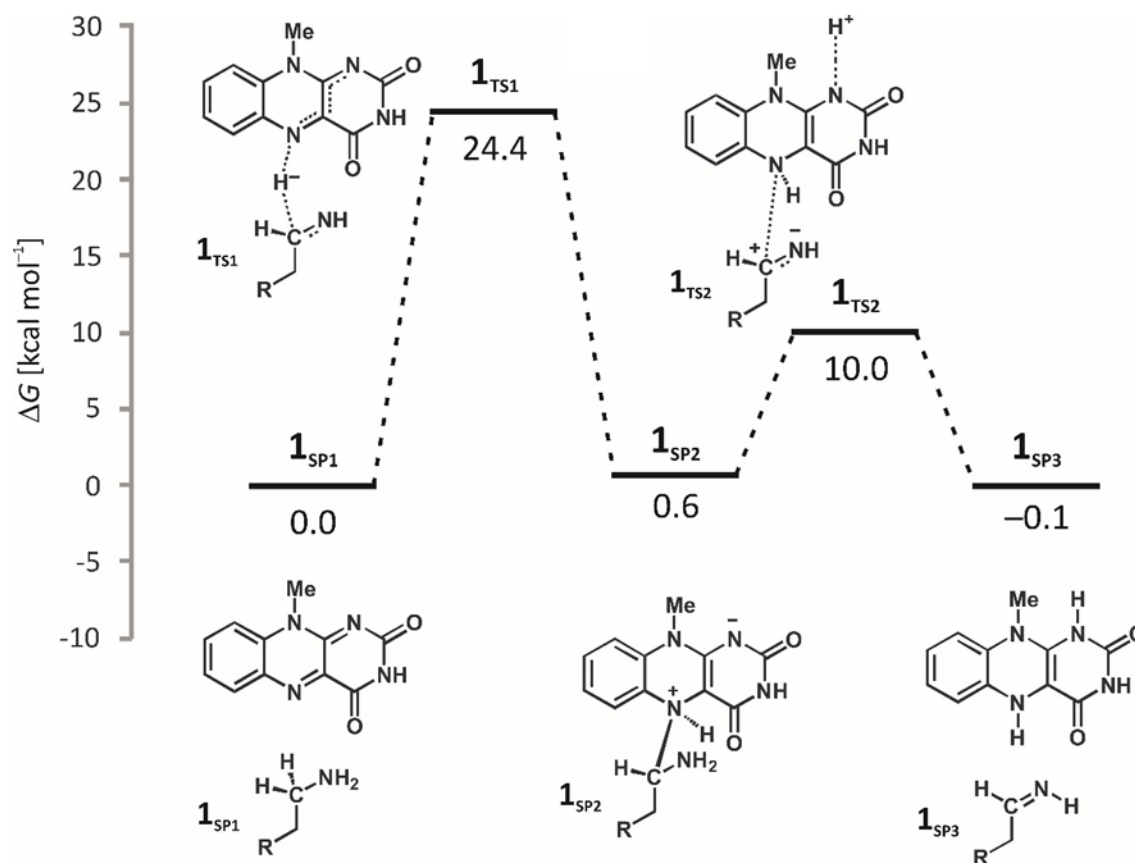
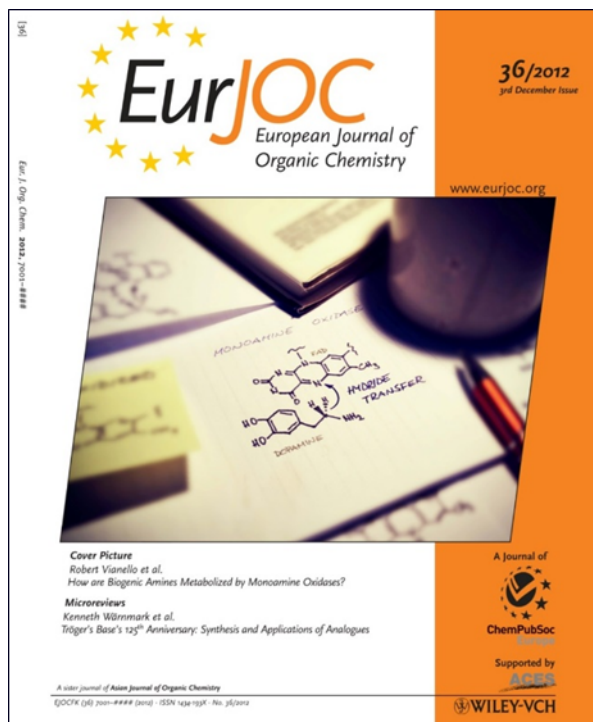
OXIDATIVE STRESS!



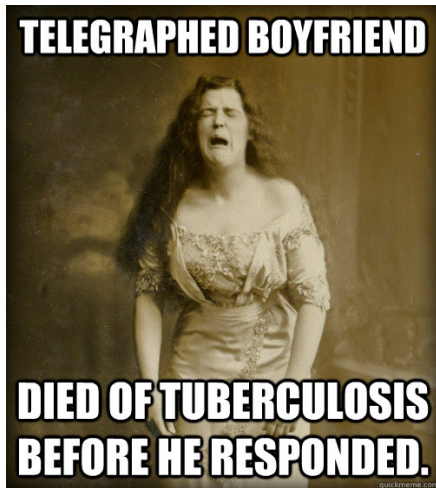
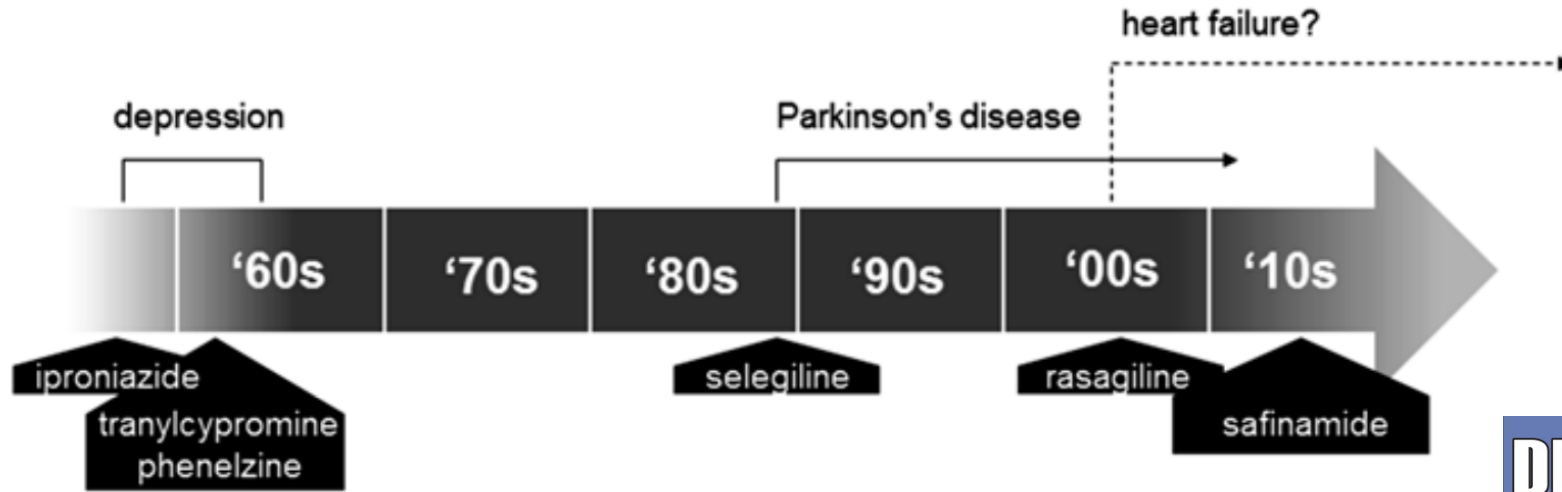
THESE APPLES DEMONSTRATE HOW OXIDATIVE STRESS BREAKS DOWN YOUR CELLS CAUSING PREMATURE AGING AND DISEASE

THE MECHANISM OF THE MAO CATALYTIC ACTIVITY

- MAO decomposes amines to imines through a **two-step hydride mechanism**



MAO INHIBITORS



The Potentiation of the Anti Akinetic Effect after L-Dopa Treatment by an Inhibitor of Mao-B, Deprenil*

W. Birkmayer, P. Riederer, M.B.H. Youdim, and W. Linauer*****

Ludwig-Boltzmann-Institut für Neurochemie, Geriatriches Krankenhaus der Stadt Wien-Lainz, Austria

With 4 Figures

Received April 25, 1975

DEPRENIL

Capsules *The mood setter*

An effective Anti-Depressant

Provides relief from :

- ♦ Anxiety
- ♦ Nervous Tension
- ♦ Irritability
- ♦ Feeling Sad
- ♦ Restlessness
- ♦ Mental Stress

Dosage : Two Capsules Twice Daily

Each 500mg Capsule contains :	
Jatamansi	Nardostachyl Jatamansi 100 mg
Jyotishmati	Celestus patriculatus 100 mg
Vacha	Acorus calamus 100 mg
Mandukaparni	Centinella asiatica 100 mg
Shankhaputpi	Convolvulus pluricularis 100 mg

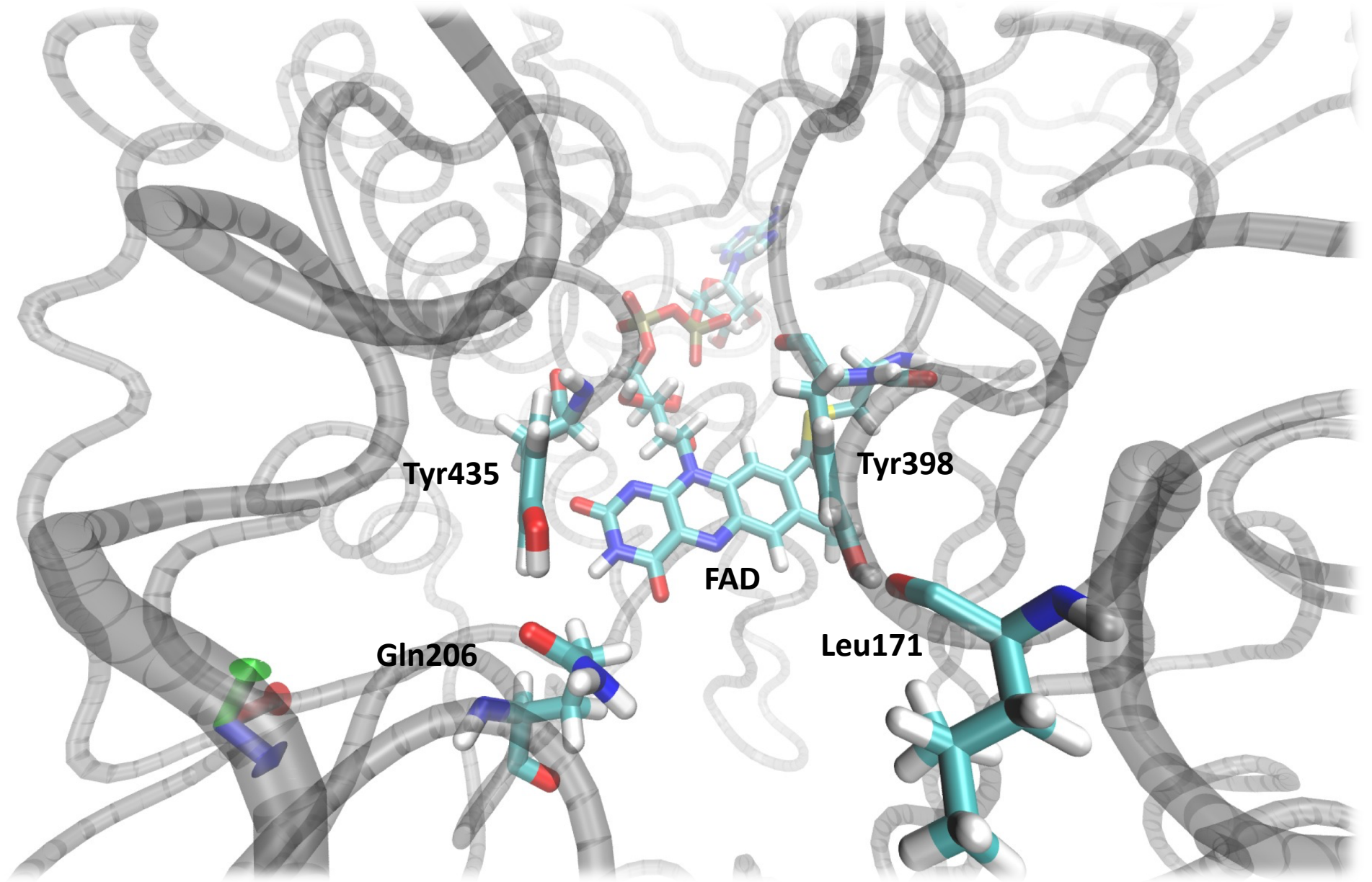
100% Natural & Herbal Dietary Supplement

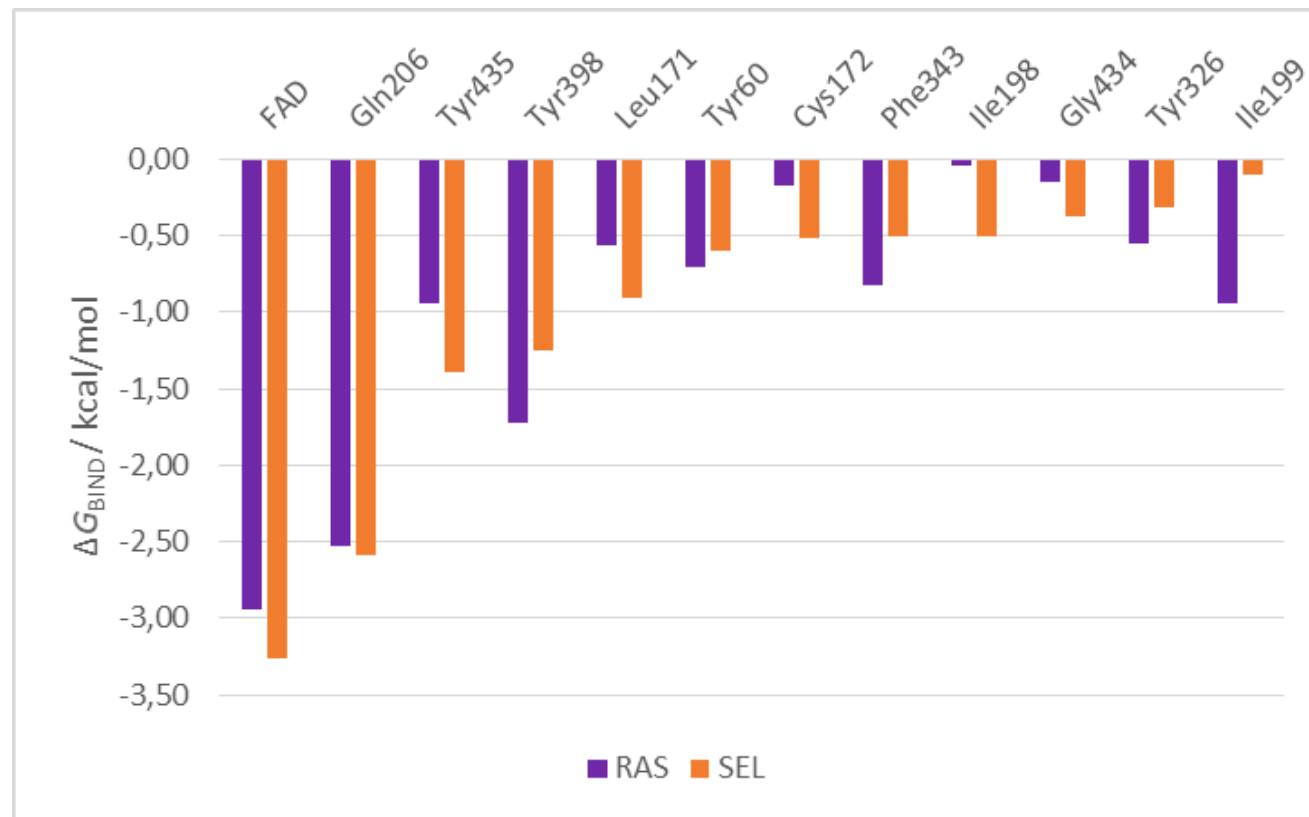
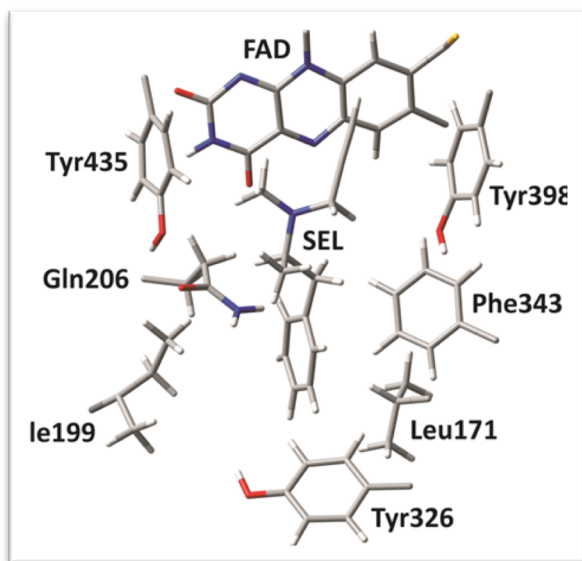
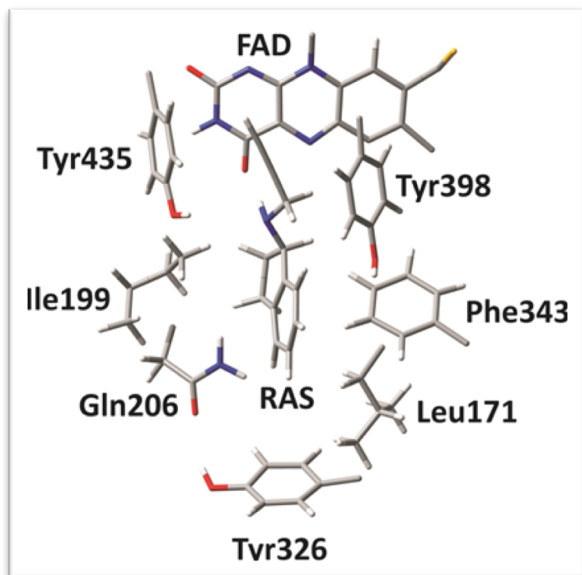
The mood Enhancer

Vasishtha
Pharmaceuticals (P) Ltd.,

MD SIMULATIONS

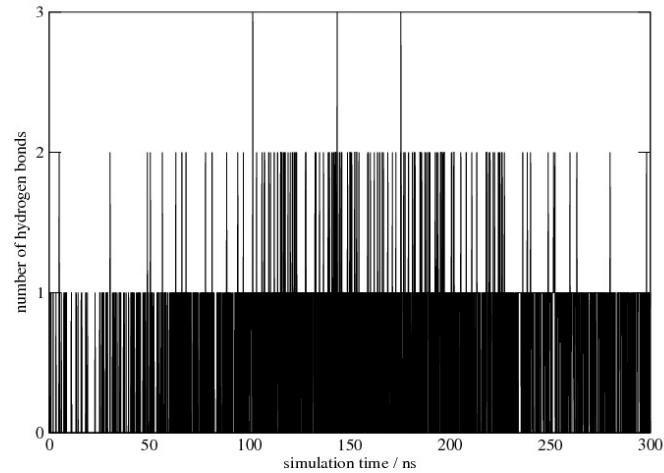
- Amber16
- 300 ns
- FF14SB, GAFF
- TIP3P type of water





	RASAGILINE	SELEGILINE
ΔG_{bind}	-30.3 kcal/mol	-31.9 kcal/mol
IC_{50}	82.5 nM	1.3 nM / 11.25 nM
K_i	700 nM	9 nM

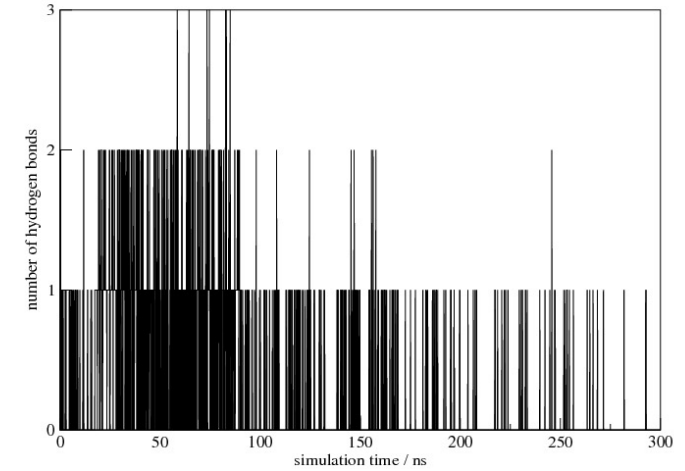
INTERACTIONS IN ACTIVE SITE



Frequency of hydrogen bonds
in active site.

RASAGILINE: 0.8 / ns

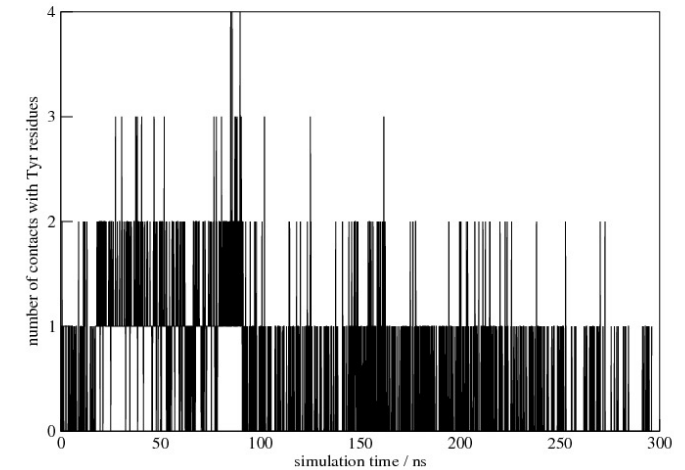
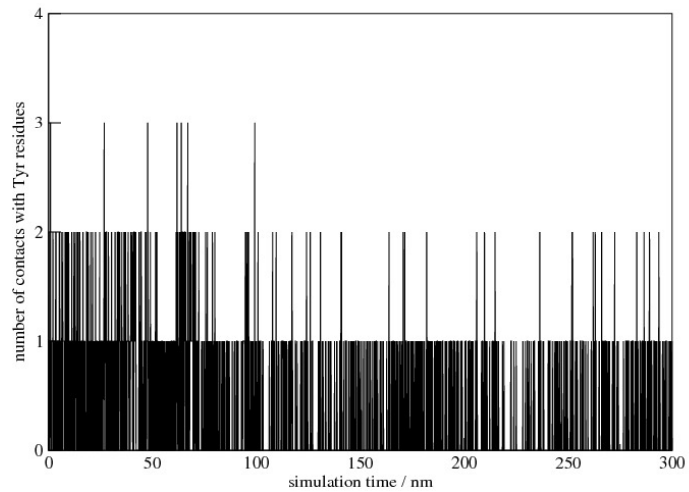
SELEGILINE: 0.2 / ns



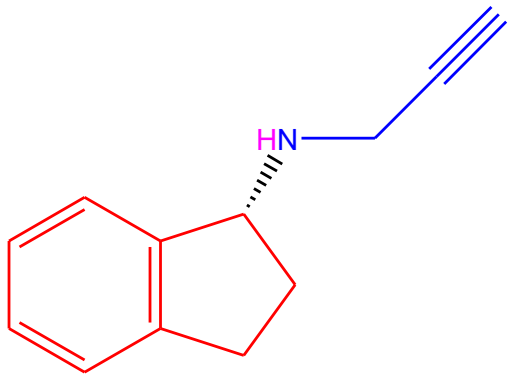
Frequency of hydrofobic interactions
with TYR in active site.

RASAGILINE: 0.34 / ns

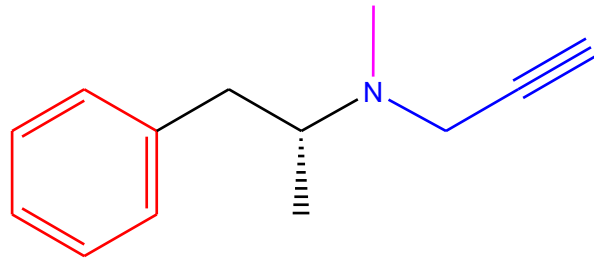
SELEGILINE: 0.51 / ns



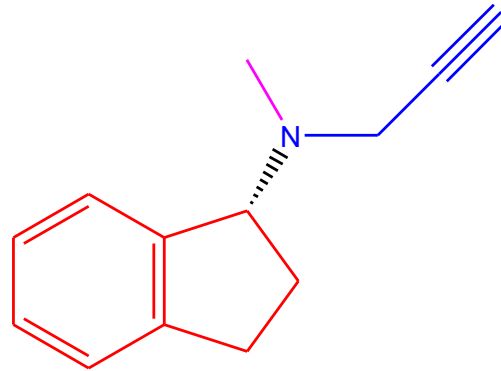
CONCLUSIONS FROM MD SIMULATIONS



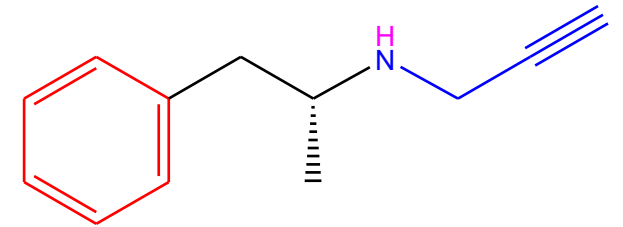
RASAGILINE



SELEGILINE



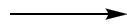
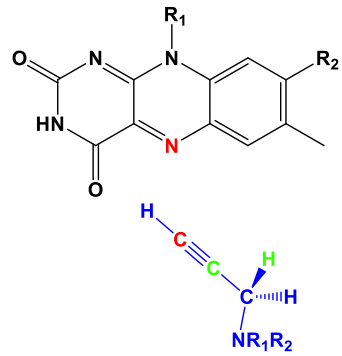
METHYL-RASAGILINE



DESMETHYL-SELEGILINE

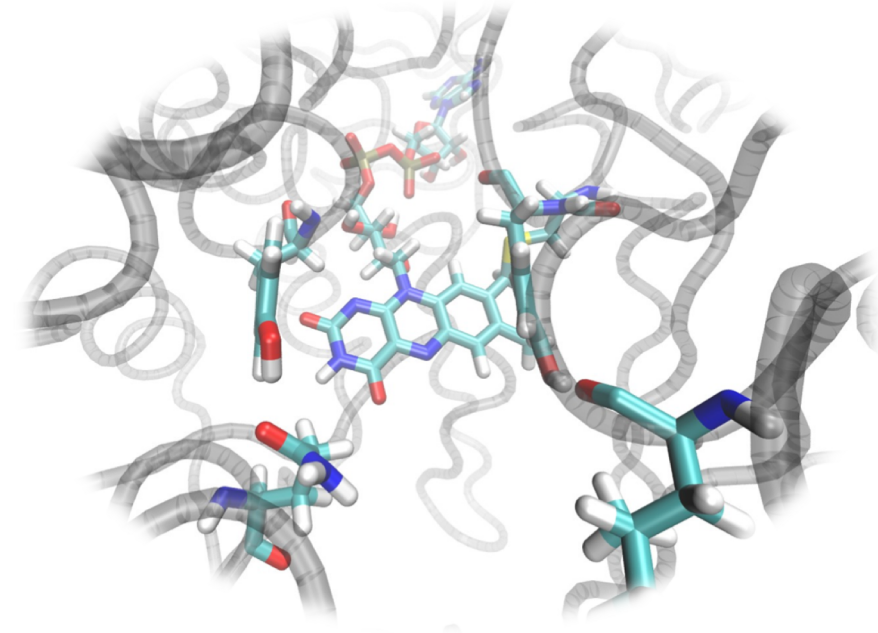
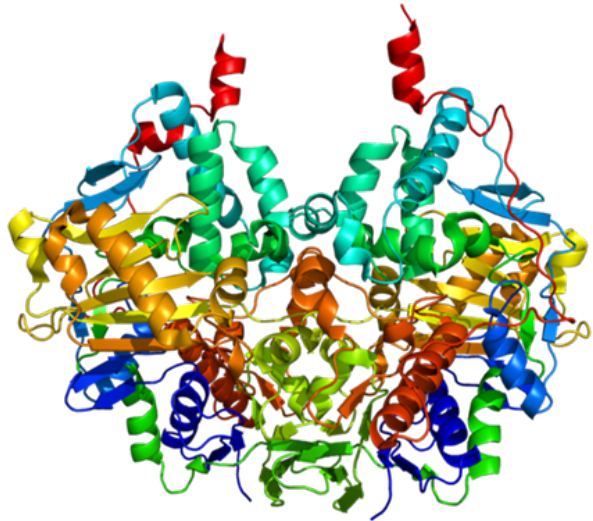
- Hydrophobic interactions are mainly responsible for binding
- Tyr435 and Tyr398 are responsible for interaction with **propargylamine** moiety
- Gln206 amine moiety interacts with **aromatic** parts of inhibitor
- Selegiline binds better than rasagiline
- Methyl group placed on amine nitrogen increases binding potential

MECHANISM OF IRREVERSIBLE INHIBITION?

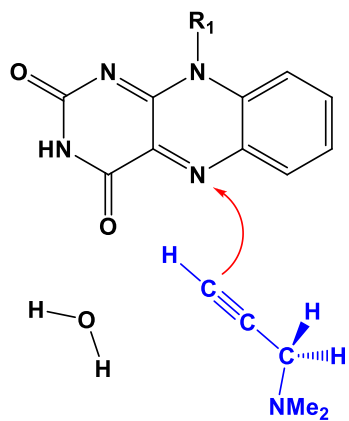


*„Not all those who wander are lost.”
J. R. R. Tolkien*

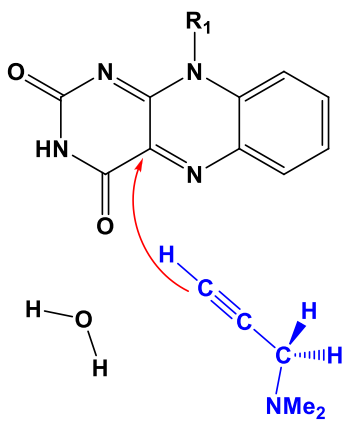
CLUSTER MODEL OF MAO B



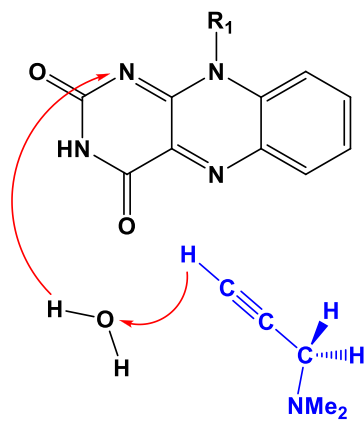
FAD
Tyr345
Tyr398
Tyr326
Tyr188
Ile199
Lys296
Cys172
Gln206



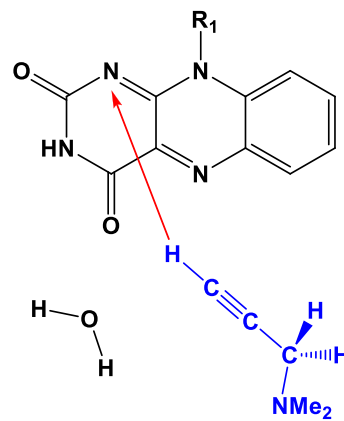
direct attack of terminal C atom to N5 of flavin



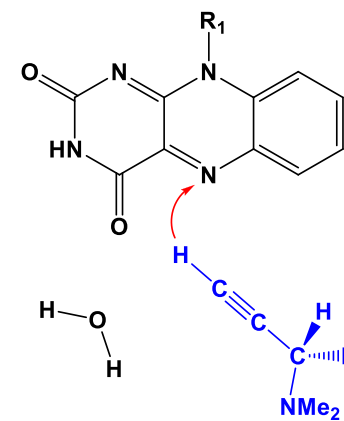
direct attack of terminal C atom to C4a of flavin



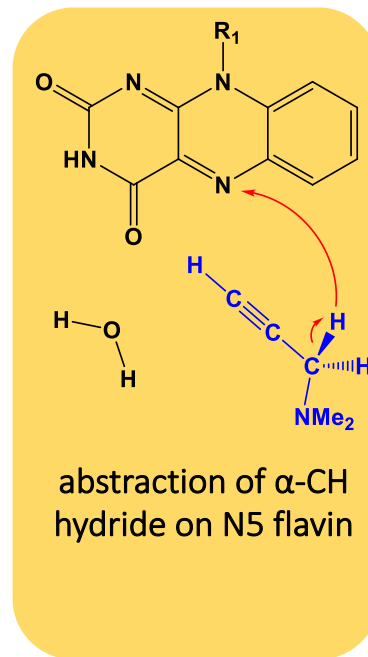
deprotonating terminal C atom with water



direct deprotonation on N1 atom of flavin



direct deprotonation on N5 atom of flavin

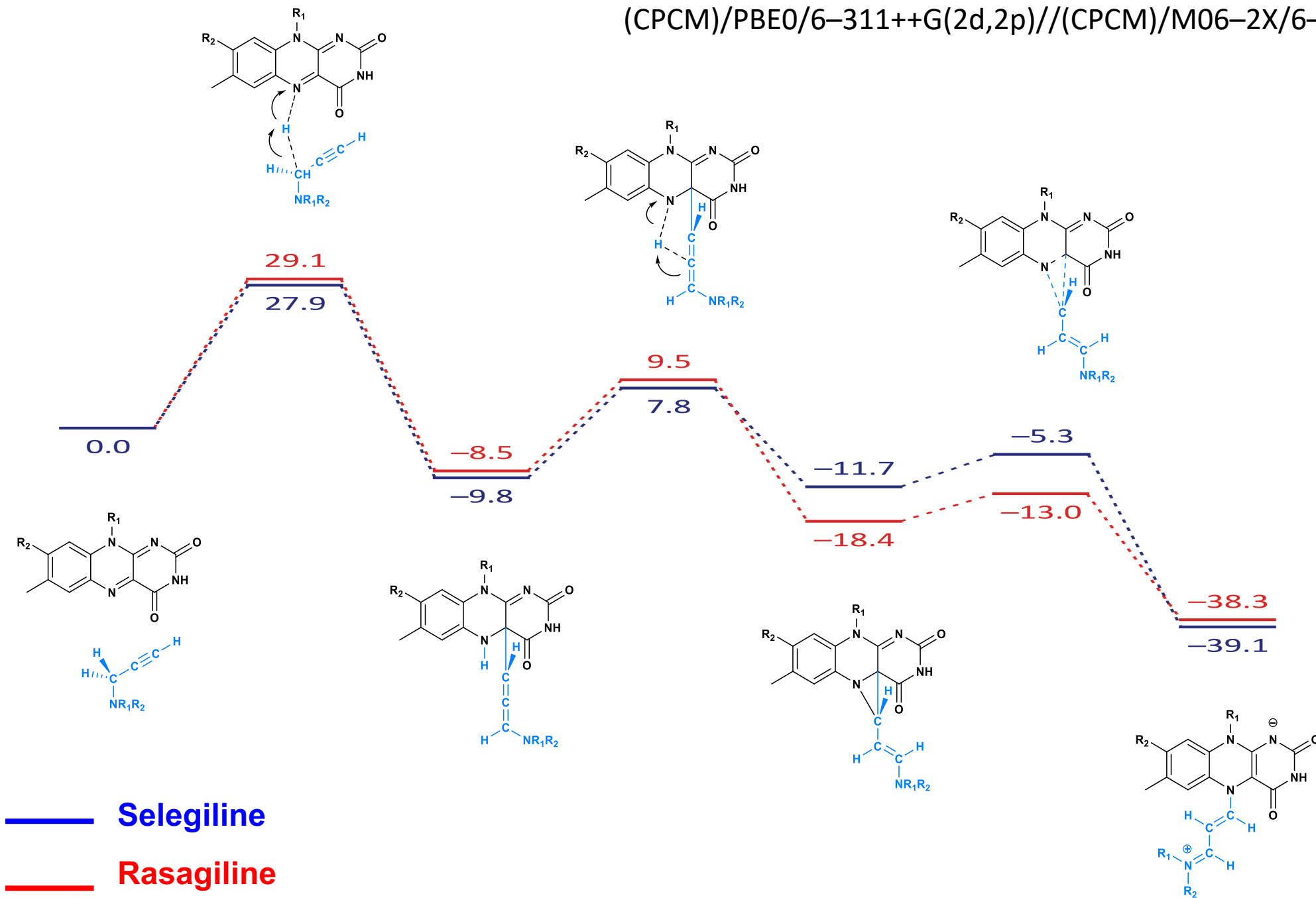


abstraction of α -CH hydride on N5 flavin

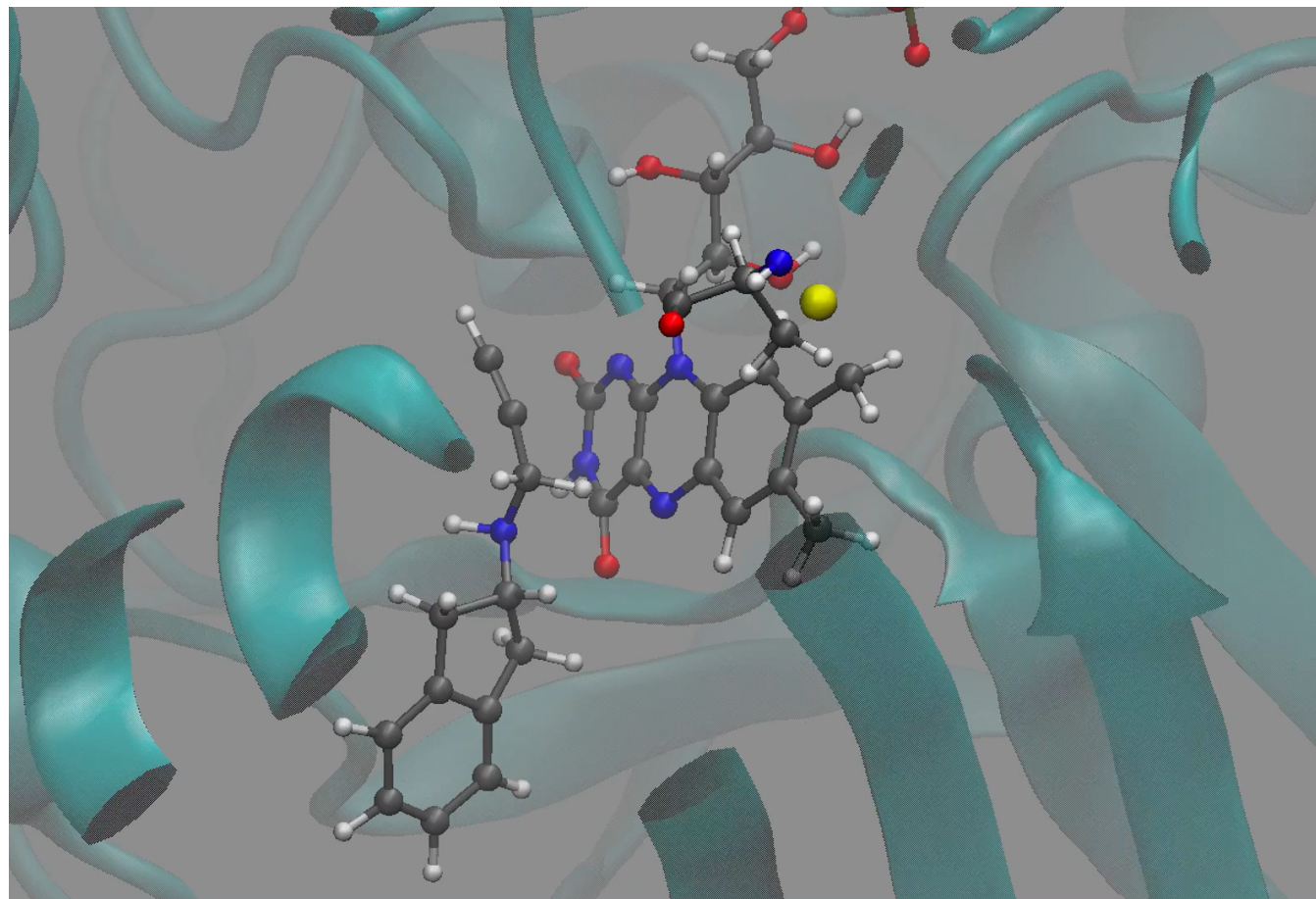


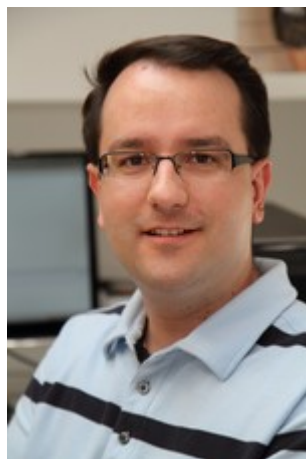
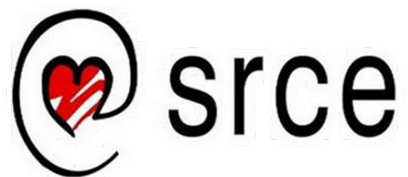


(CPCM)/PBE0/6-311++G(2d,2p)//(CPCM)/M06-2X/6-31+G(d,p)



EMPIRICAL VALENCE BOND (EVB) SIMULATIONS – IN PROGRESS





Robert Vianello
Ruđer Bošković
Institute
Zagreb



Janez Mavri
Institute of Chemistry,
Ljubljana, Slovenia



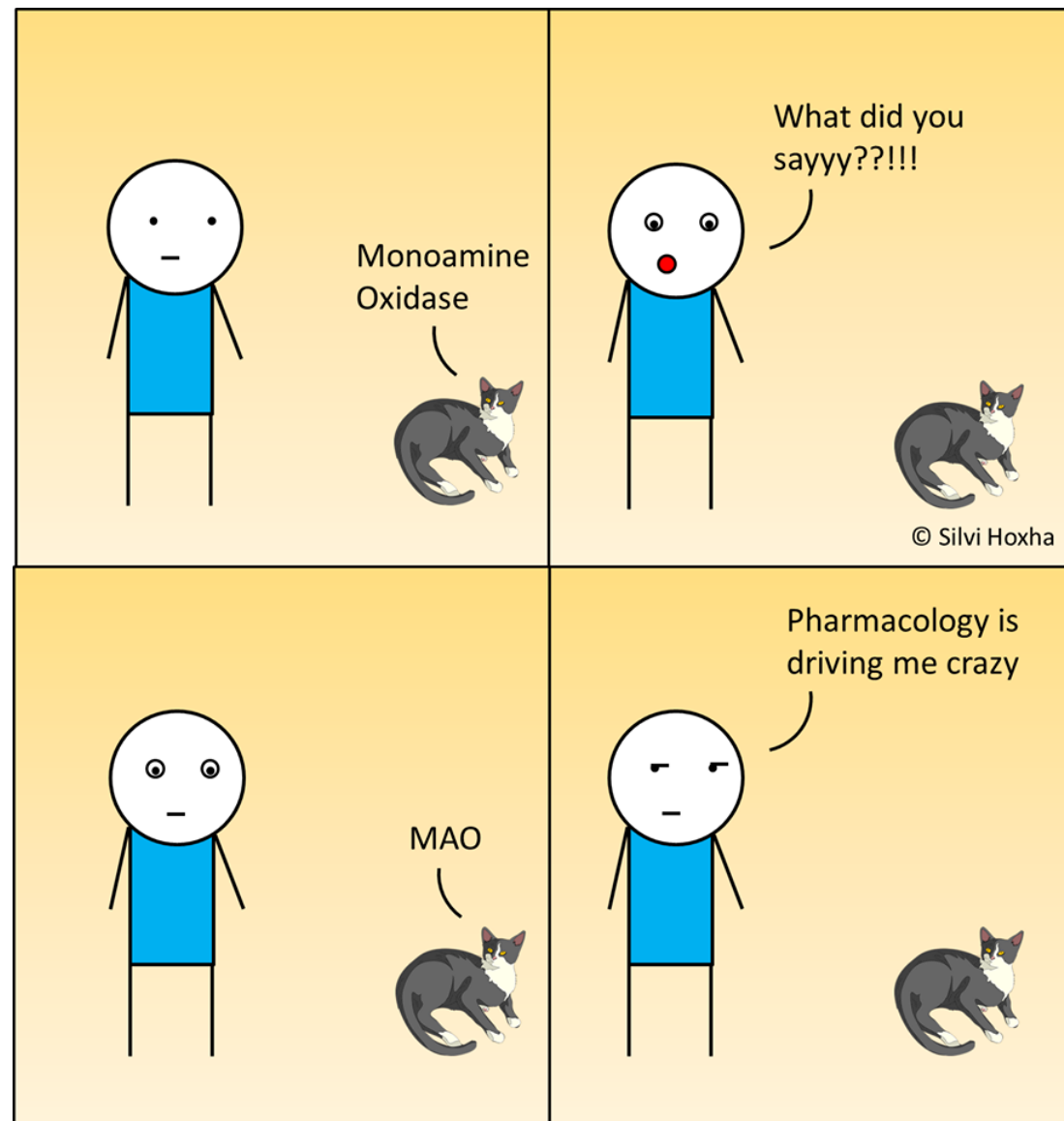
Jernej Stare
Institute of Chemistry,
Ljubljana, Slovenia



Lucija Hok
Ruđer Bošković Institute
Zagreb



Alja Prah
Institute of Chemistry,
Ljubljana, Slovenia



QUESTIONS?

