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VIRTUAL SCREENING OF COMPOUNDS BY CHEMOINFORMATICS TOOLS IN THE CHEMISTRY LABS

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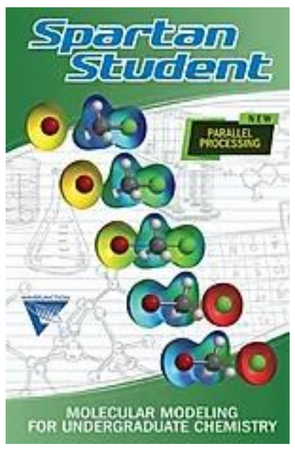
COMPUTATIONAL PROCEDURE



- ✓ 3D stucture generation
- ✓ Geometry optimization: energy minimization, MMFF
- ✓ Density functional theory (DFT), Möller-Plesset (MP2) methods
- ✓ Functionals: B3LYP (a global hybrid functional) or improved functionals (ωB97X-D, ωB97X-V and M062X) [1,2]
- ✓ Equilibrium geometry at ground state
- ✓ Spartan Software, Wavefunction Inc, Irvine, CA, USA [2]
- ✓ Molinspiration online platform: calculation of molecular properties and bioactivity scores

Global reactivity parameters / Koopmans' theorem [3]	
FMOs energy gap	ΔE (E_{HOMO}-E_{LUMO}) (eV)
Ionization potential	$I = - E_{HOMO}$ (eV)
Electron affinity	$A = - E_{LUMO}$ (eV)
Electronegativity	$x = (I + A)/2$ (eV)
Global hardness	$\eta = (I - A)/2$ (eV)
Local softness	$\sigma = 1 / \eta$
Chemical potential	$m = (E_{HOMO}+E_{LUMO})/2$
Global electrophilicity index	$\omega = \mu^2 / 2\eta$

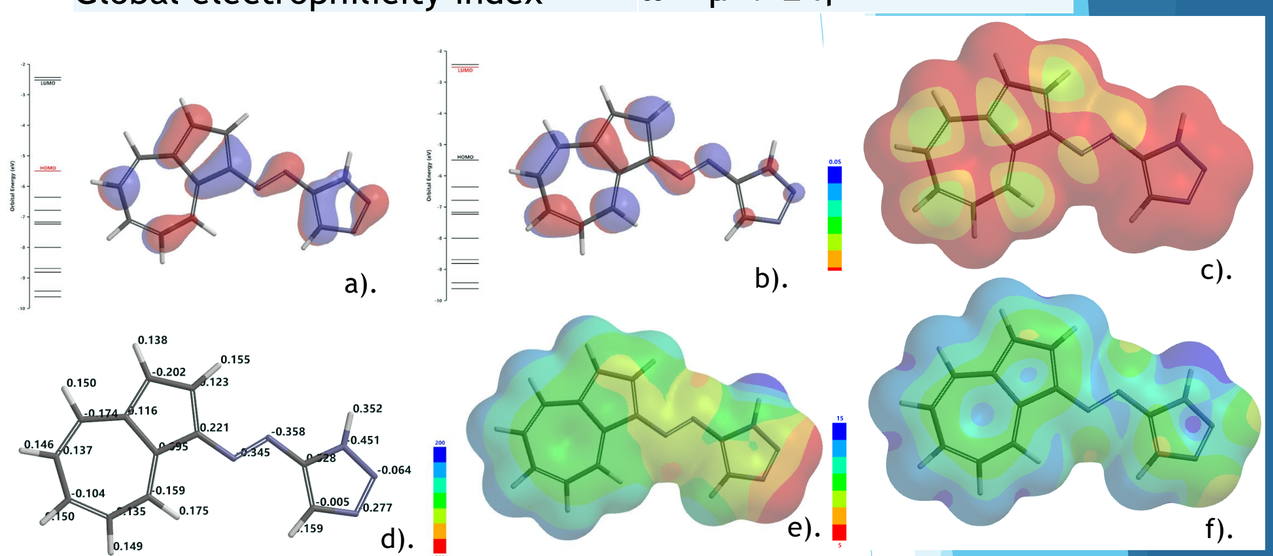


Fig. 1 a) HOMO energetical level; b) LUMO energetical level; c). LUMO map; d) Mulliken charges; e) Electrostatic potential map; f). Local ionization potential map

ELECTROCHEMISTRY

Bredas et all's empirical equations [6]:

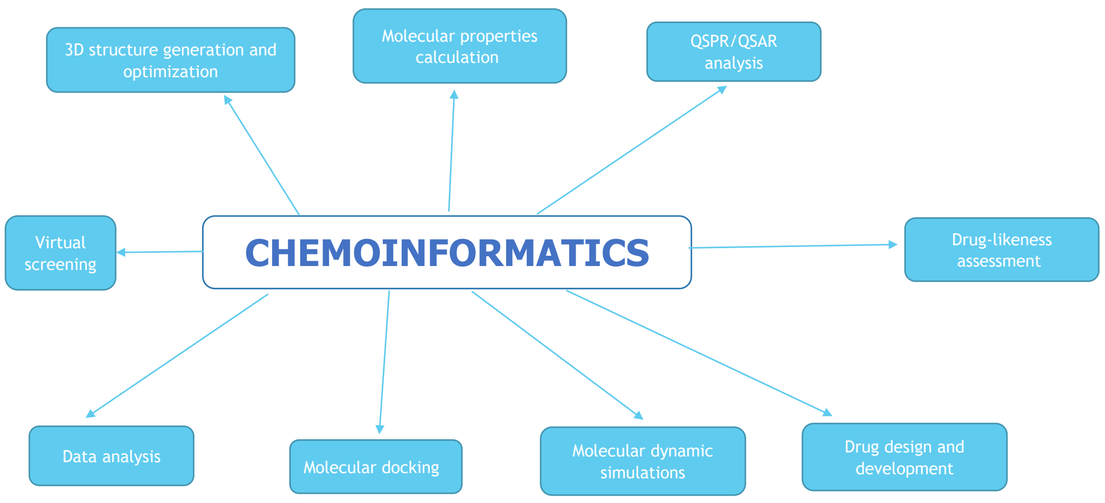
$$E_{HOMO} = -e\,[E_{ox}^{onset} + 4.4]$$
$$E_{LUMO} = -e\,[E_{red}^{onset} + 4.4]$$

Marcus quadratic relationship for interfacial electron transfer [7]:

$$E_{OX/RED} = a + b \cdot E_{HOMO/LUMO}$$

where $E_{OX/RED}$ are the experimental redox potentials; $E_{HOMO/LUMO}$ the calculated HOMO and LUMO energies; and a and b are constants.

Literature:
- ✓ linear relations between the experimentally measured reduction potential of a series of some ß-diketones and their calculated LUMO energies and *E* [7]
- ✓ linear relationship between oxidation potential and calculated HOMO energies and *I*, respectively [7]
- ✓ complexing capacity and potential use of various ligands for toxic transition metals [8]



ASSESSMENT OF ORAL BIOAVAILABILITY

LIPINSKI'S RULE OF FIVE (RO5) (PFIZER) [4]

MW < 500 Da
LogP < 5
HBD < 5
HBA < 10

Veber and co-workers [5]:

PSA < 140 Å^2
No of rotatable bonds: < 10

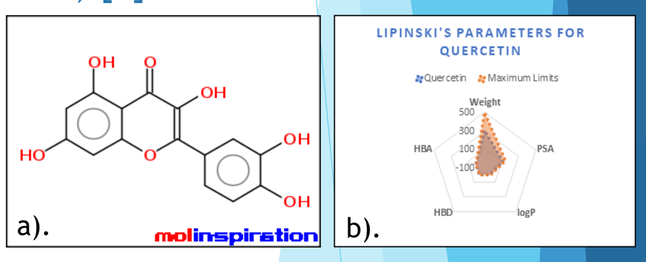


Fig. 2 a) Quercetin structure; b). computed drug-likeness parameters for Quercetin

molinspiration
cheminformatics

BIOACTIVITY SCORES reported to common human target proteins:

- ✓ GPCR ligands
- ✓ ion channel modulators
- ✓ kinase inhibitors
- ✓ nuclear receptor ligands

Molinspiration bioactivity score v2018.03	
GPCR ligand	-0.06
Ion channel modulator	-0.19
Kinase inhibitor	0.28
Nuclear receptor ligand	0.36
Protease inhibitor	-0.25
Enzyme inhibitor	0.28

Predicted Quercetin's bioactivity scores

CONCLUSIONS AND PERSPECTIVES

- ✓ **From frontier molecular orbital energies (FMOs), the reactivity and kinetic stability can be assessed in accordance with their energy gap;**
- ✓ **The accuracy of the predictions can be verified by comparing predicted and experimental chemical shifts from RMN data.**
- ✓ **From calculated HOMO and LUMO energies, redox potentials can be predicted and consequently, the complexing capacity with regard to heavy metals such as cadmium, copper, lead, nickel, and zinc, for electrochemical applications**
- ✓ **QSPR/QSAR analysis and drug-likeness parameters assessment can be easily realized for large compound libraries, by means of chemoinformatics tools**

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REFERENCES

[1] W.J. Hehre, A Guide to Molecular Mechanics and Quantum Chemical Calculations, Wavefunction, Inc., Irvine, CA, 2003
[2] Y. Shao, L.F. Molnar, Y. Jung, et al., Advances in methods and algorithms in a modern quantum chemistry program package, Phys. Chem. Chem. Phys.2006, 8, 3172-3191
[3] T. Koopmans, Über die Zuordnung von Wellenfunktionen und Eigenwerten zu den Einzelnen Elektronen Eines Atoms, Physica 1934, 1(1–6):104-113
[4] C.A. Lipinski, Lead-and drug-like compounds: the rule-of-five revolution, Drug Discovery Today: Technologies 2004, 1(4):337-341
[5] D.F. Veber, S.R. Johnson, H.Y. Cheng, B.R. Smith, K.W. Ward, K.D. Kopple, Molecular properties that influence the oral bioavailability of drug candidates, J. Med. Chem. 2002, 45 (12): 2615-2623
[6] J.L. Bredas, R. Silbey, D.S. Boudreux, R.R. Chance, Chain-length dependence of electronic and electrochemical properties of conjugated systems: polyacetylene, polyphenylene, polythiophene, and polypyrrole, J. Am. Chem. Soc. 1983, 105(22): 6555 – 65594
[7] J. Conradie, A Frontier orbital energy approach to redox potentials, J. Phys.: Conf. Ser. 2015
[8] A. Stefaniu, M.-D. Pop, G.-L. Arnold, L. Birzan, L. Pintilie, E. Diacu, E.-M. Ungureanu, DFT calculations and electrochemical studies on azulene ligandsfor heavy metal ions detection using chemically modified electrodes, J. Electrochem. Sci. Eng. 2018, 8:73-85